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RENAL NEOPLASMS IN YOUNG CHILDREN*

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In young children renal new growths are encountered often enough to make their study of interest, and experience at the Babies' Hospital teaches that primary neoplasms occur more frequently in the kidney than in any other organ. Eighteen such tumors form the basis of this study. They occurred in children from 3¾ months to 6 years of age. Seven were less than 1 year old, and two were over 3 years, leaving nine patients between the ages of 1 and 3 years. Ten were girls and eight were boys. Ten tumors involved the right kidney, and eight the left.

Certain features were common to all the neoplasms: they were unilateral, retroperitoneal and within the kidney capsule, and compressed the kidney substance so that a layer of fibrous tissue from which all renal structures had been eliminated separated the kidney from the new growth. In the compressed kidney near the periphery of the tumor, dilated tubules and glomeruli were present in several cases. Whether these were due to the pressure of the new growth, or whether they antedated the neoplasm it is not possible to decide. The former would seem more plausible.

The neoplasms may grow in any portion of the kidney. Thus, four occupied the lower pole, two the upper pole, four the kidney pelvis, three the anterior surface, one the posterior surface, and two the outer border, and two were surrounded by thinned kidney substance as by a pair of open tongs. In no instance was the kidney entirely separate from the neoplasm. The attachment was always intimate, whether over a small area at one pole or over one entire surface, and it was not possible to separate the kidney from the tumor without leaving some renal tissue in the neoplasmic mass. Hedren's [1] case is unusual, in that bilateral rhabdomyo-adenosarcomas could be shelled out, leaving the kidney substance compressed but not infiltrated.

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1. Hedren, G.: Zur Kenntniss der Pathologie der Mischgeschwülste der Nieren, Beitr. z. path. Anat. u. z. allg. Pathol. **40**:1, 1906-1907.

Quite different were six primary neoplasms of the suprarenal, which were entirely outside and above the kidney, leaving its shape unaltered, except where the upper pole was cupped to receive the tumor. Borst [2] refers to an extrarenal mixed tumor of the kidney which came under his observation.

The degree of kidney change in shape and size varied from depression of one border or surface, or the loss of half or more of the kidney substance from one pole, or from the pelvis, to such marked compression that a rim of kidney substance, 0.5 cm. or less, formed a capsule for most of the growth. The adenosarcomatous tumors in the kidney pelvis were papillary in type.

The consistency of the new growths varied. Nine were quite firm, and were removed entire, as a more or less globular or oval mass, nodular in all but two, surrounded by an intact capsule within which the kidney and the neoplasm were found. Nine others were soft, fluctuating in places. In seven instances the distended capsule gave way at operation, spilling soft tumor masses and altered blood. On section the firmest growths had an even, pink or gray, lobulated appearance, with little or no hemorrhage or softening. In others the cut section showed, in addition to lobulated areas of fairly firm consistency, younger portions which were medullary in appearance, with fresh and old hemorrhages, some contained in cystlike cavities. The whole surface varied from white to dark red. The largest mass removed at operation weighed 3,750 Gm.; the smallest weighed 170 Gm.

Microscopically the neoplasms were all embryonal in type. One was an unmixed spindle cell sarcoma, thirteen were adenosarcomas, three were leiomyo-adenosarcomas and one was a rhabdomyo-adenosarcoma.

SPINDLE CELL SARCOMA

The only example of this type of neoplasm occurred in a boy, aged 6 months, admitted eighteen days after his abdominal tumor had been noticed. He recovered from the operation, at which a mass measuring 22.5 cm. in circumference, and 9.5 by 5.5 cm. in diameter was removed. The irregularly round tumor was surrounded by a capsule except at its most dependent part, where rupture had taken place, and fluid contents had been lost. The neoplasm grew in the pelvis of the kidney, compressing the pyramids and cortex to a width varying from 1 to 3 cm. Unlike the adenosarcomas of the kidney pelvis, which are papillary in type, the neoplasm was firm, smooth and white. No ureter was found. Microscopic examination proved that the neoplasm was composed of spindle shaped cells with comparatively large nuclei, arranged in whorls around blood vessels (fig. 1). The latter were numerous, with thin walls.

2. Borst, M.: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902.

Many spindle cells showed mitotic figures. The connective tissue stroma was small in amount. At the periphery of the tumor it was edematous, and acted as a capsule between the tumor and most of the compressed kidney substance, which was invaded by the growth at several points. Section through the kidney showed no lesion beyond the compressed area, but there the growth was locally invasive. It not only compressed the kidney parenchyma, but also grew into it from the pelvis. While three dilated calices were present, there was no outlet from these into a pelvis and ureter.

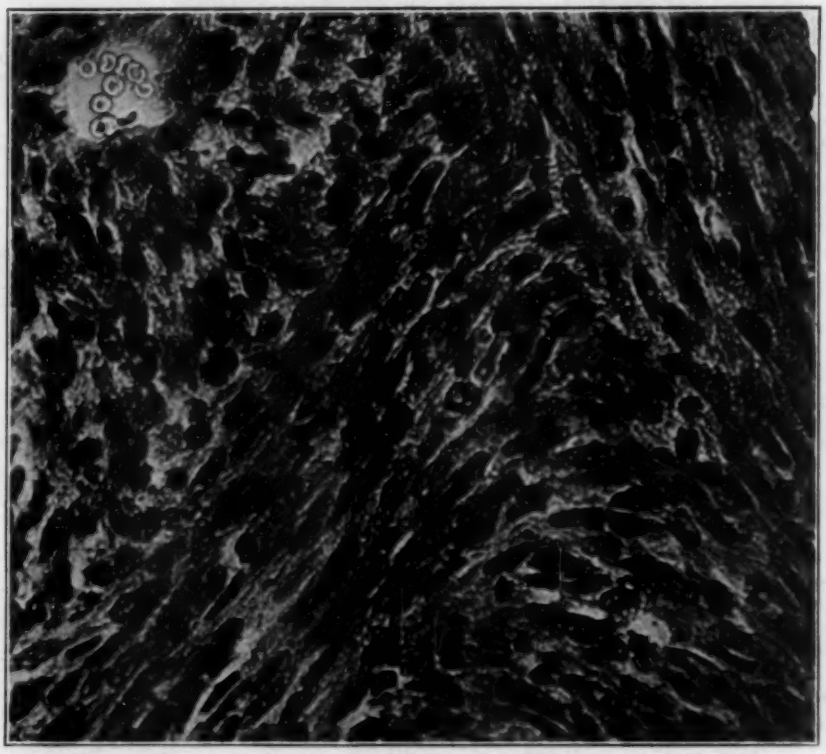

Fig. 1.—Spindle cell sarcoma in a boy, aged 6 months; the growth recurred after one month; × 600.

The patient was readmitted two and one half months after operation, because a recurrent growth had appeared six weeks before. This neoplasm recurred more rapidly than did any other tumor of the series. Jaundice developed, and the child died three months after operation, or three and one half months after the onset of symptoms. At necropsy a recurrent tumor, 780 Gm. in weight, was found behind the peritoneum in the region of the right kidney and median line. The liver was so compressed that it measured only 1 cm. in thickness, and the under sur-

face of its right lobe was adherent to the tumor mass. The left kidney was much enlarged. The macroscopic and microscopic character of the recurrent tumor was identical with that of the primary growth. The enlarged left kidney showed no lesion except a moderate amount of epithelial degeneration. Compression of the bile ducts on the under surface of the liver accounted for the jaundice. No metastases had developed, only a local, large recurrence.

A spindle cell sarcoma of the kidney occurring in a stillborn seven months fetus has been reported by Kastner.[3] Mixter[4] observed one such case among twenty-two renal neoplasms. Ribbert[5] found that spindle and round cell sarcomas of the kidney in children are rare.

EMBRYONAL ADENOSARCOMA

Birch Hirschfeld[6] introduced the term embryonal adenosarcoma to designate the group of embryonal cell tumors of the kidney in young subjects composed of tubular (epithelial) and connective tissue (sarcomatous) elements He pointed out that some of the growths contain striated or unstriated muscle cells or both, and to these he applied the term embryonal adenomyosarcoma.

Broadly the neoplasms studied were composed of (*a*) masses of embryonal round or spindle cells, with deeply staining nuclei showing many mitoses, arranged in solid masses outlined by a delicate stroma of thin fibrous or myxomatous tissue carrying blood vessels, and (*b*) round or slightly polyhedral cells with hyperchromatic and mitotic nuclei forming round or long ovoid masses in which lay tubules lined with cuboidal or cylindrical epithelium. It was in the proportion of these two types of elements, manifestly epithelial and sarcomatous, in their arrangement and in their relation to each other, that each tumor showed distinct characteristics, while maintaining the group traits; in consequence, subdivision of the seventeen adenosarcomas may be made as follows:

1. The second largest tumor of all the eighteen, and the largest removed by operation, was firm and was removed without any break in the capsule. Its most prominent feature was striated muscle fibers running in all directions (fig. 2). Between these were many small, round

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3. Kastner, H.: Nierensarkom bei einem sieben monatlichen Fötus, Frankfurt. Ztschr. f. Path. **25**:1, 1921.

4. Mixter, C. G.: Tumors of the Kidney in Infancy and Childhood, Ann. Surg. **76**:52, 1922.

5. Ribbert and Mönckeberg: Lehrbuch der allgemienen Pathologie, Leipzig, F. C. W. Vogel, 1923.

6. Birch Hirschfeld, F. V.: Sarkomatose Drüsengeschwülst der Niere im Kindesalter (Embryonales adenosarkom), Beitr. z. path. Anat. u. z. allg. Pathol. **24**:343, 1898.

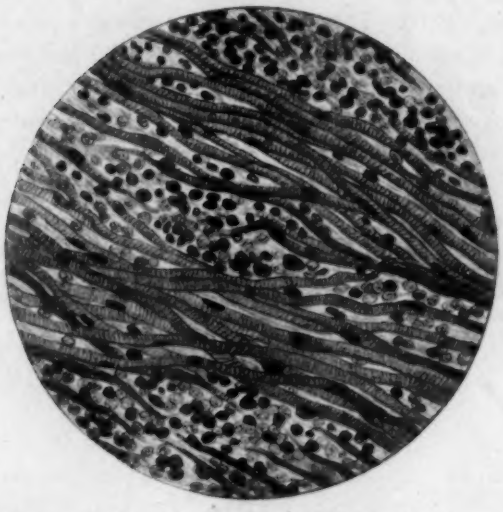

Fig. 2.—Striated muscle fibers and undifferentiated round cells in a rhabdomyo-adenosarcoma in a girl, aged 14 months; permanent recovery; the tumor weighed 3,750 Gm.

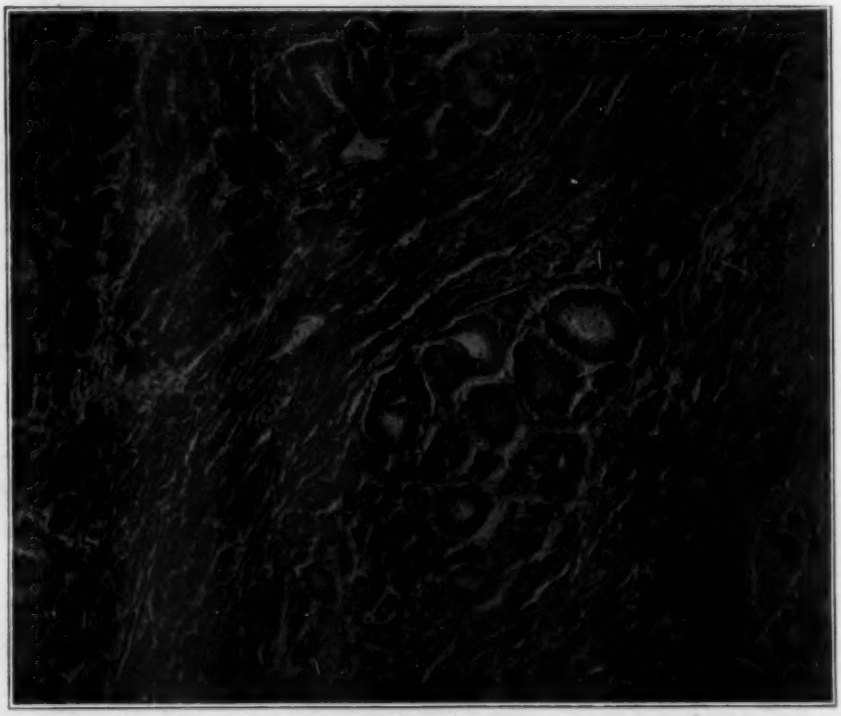

Fig. 3.—Neoplasm largely adenomatous in type with small areas of undifferentiated round cells in a girl, aged 9 months who died of hemorrhage four hour after operation; the tumor weighed 560 Gm.; × 300.

and spindle shaped cells. There were also embryonal tubules and embryonal glomeruli in all stages of development. All these elements were most irregularly mixed, but gave the impression of firmness. No areas of necrosis, hemorrhage or cysts were present. It was a rhabdomyoadenosarcoma, a mixed tumor of Wilms.[7] The case of the girl from whom this tumor was removed when she was 14 months old has been reported,[8] and she is still alive and well. Hedren [1] likens the rhabdomyosarcomas of the kidney to fibromyomas of the uterus in the firmness of their gross appearance.

2. Two tumors were composed chiefly of tubules lined with one or several layers of columnar epithelial cells, lying on a thin basement membrane. These tubules varied in size and shape, and there were also long striae resembling the collecting kidney tubules, which served to divide the growth into areas suggestive of the medullary pyramids of the normal kidney (fig. 3). The stroma between the tubules was small in amount, but there were solid masses of undifferentiated, round cells dividing rapidly. Both tumors were solid, surrounded by a capsule of compressed kidney, with one small wedge-shaped mass in which pelvis, medulla and cortex were still preserved. The origin of the tumors was probably in the lower pole of the kidney. The tubular structure was by far their most prominent feature, and they were the most adenomatous growths encountered. One of the children died of hemorrhage four hours after the operation. The other was discharged in excellent condition, but could not be traced for final report.

3. Six neoplasms were composed partly of tubules arranged in lobules, and partly of areas made of round and spindle cells packed into solid masses without any evidence of a lumen or of tubule formation (fig. 4). The nuclei of the cells showed many mitotic figures. The tumors were firm, the capsule remained unbroken at operation, and on section they showed solid, pink lobules and some darker areas of hemorrhage. These neoplasms were more largely sarcomatous than were the growths of the second type, and while their adenomatous portion was extensive, it was no longer their main feature. The youngest child in our series, 3¾ months old, belongs in this subgroup, and is now a healthy girl, aged 7 years. Another child is well ten months after operation, although the growth had extended into the renal vein as a papillomatous mass to a distance of 1 cm., the vena cava being free. One patient cannot be traced; one died four days after operation, and another fifteen months afterward, with recurrence and lung metastases. One tumor was removed after death, and proved to be the largest encountered at the Babies' Hospital, weighing 4,000 Gm. The child's weight was 7,300 Gm.

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7. Wilms, M.: Die Mischgeschwülste, Leipzig, Arthur Georgi, 1899.

8. Abbe, R.: Sarcoma of the Kidney; Its Operative Treatment, Ann Surg. **19**:58, 1894. Wollstein, M.: Proc. N. Y. Path. Soc., 1893, p. 123.

4. The growths of the fourth type were made of large, irregular masses of embryonal round and spindle cells, more round than spindle, less differentiated, and rapidly dividing. Groups of embryonal tubules and glomeruli were present, but scattered (fig. 5). The stroma between the masses of embryonal cells was myxomatous or delicately fibrous, and unstriated muscle cells (fig. 6) were found in two of the seven cases in

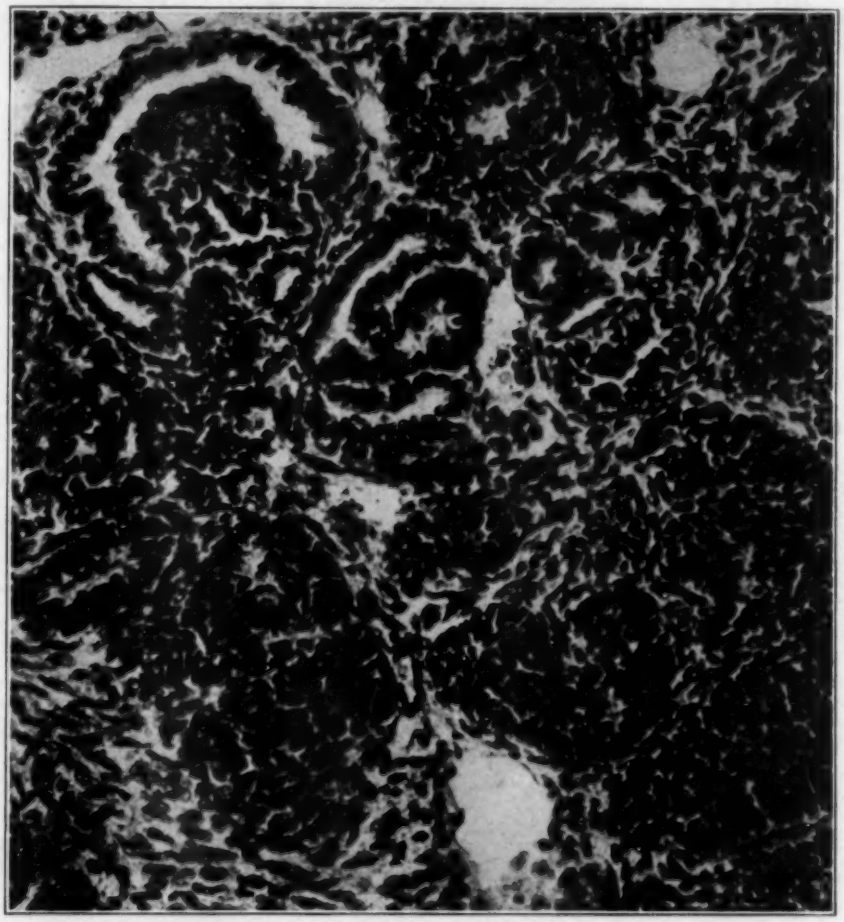

Fig. 4.—Tubules, glomeruli and alveoli filled with embryonal round cells; also an area of spindle cells; × 300.

the group. These tumors were far more sarcomatous than adenomatous, and the lack of differentiation of the cells forming the bulk of the growth was their prominent feature. They were irregularly nodular, soft and pink, yellow or gray in places, and at operation the capsule tore. Three of the seven patients in this subgroup showed locally recurring

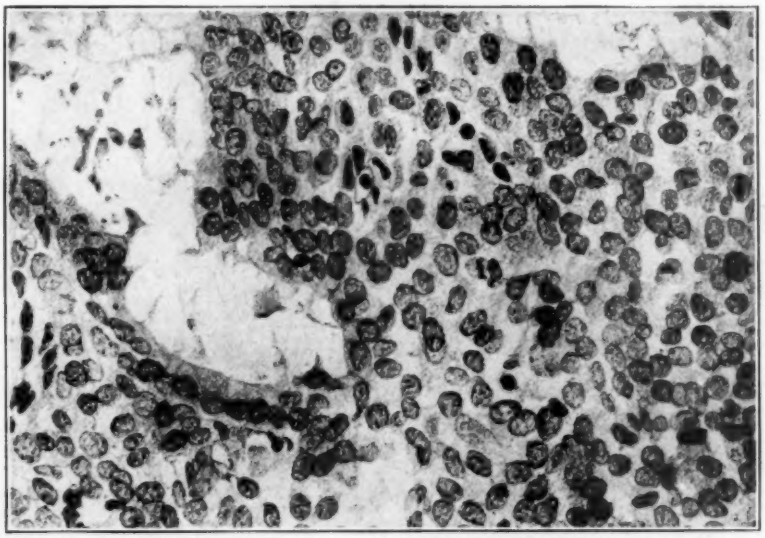

Fig. 5.—Neoplasm composed almost entirely of undifferentiated round cells, and irregular tubules lined with flattened epithelial cells.

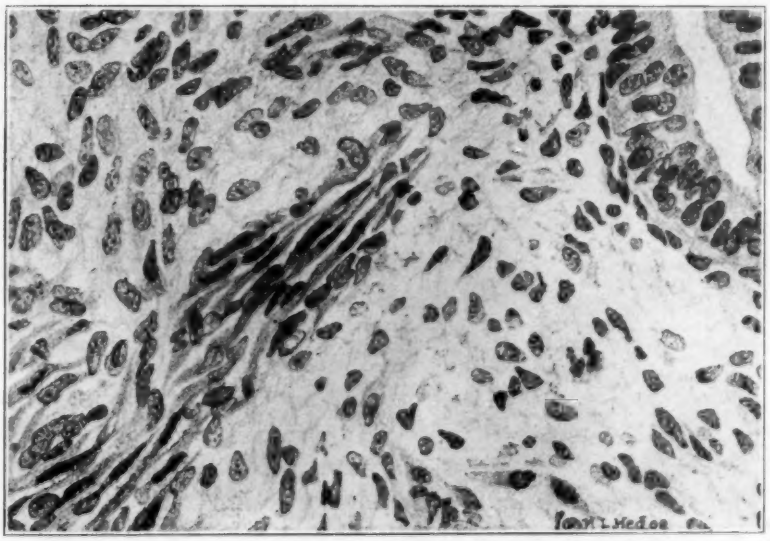

Fig. 6.—Unstriated muscle cells in neoplasm weighing 170 Gm.

growths one to seven months after operation, and at necropsy metastases were found in the lungs and liver in one instance, in the liver alone in another and in the lungs alone in the third. One boy died of shock during the operation; one died at home four months afterward, and one could not be traced.

5. Finally, one neoplasm differed from all the others in that its embryonal epithelial cells were so numerous and so arranged that the

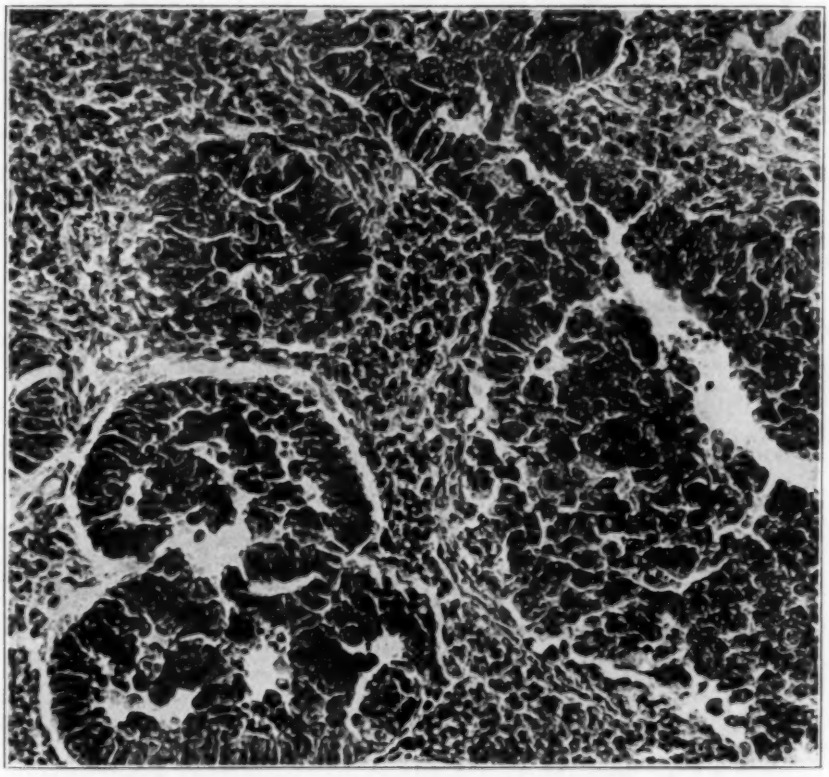

Fig. 7.—Epithelial cells in solid alveoli and around an irregular lumen; large groups of undifferentiated, round cells. The patient, aged 6 years, died about three months after the removal of a fluctuating neoplasm weighing 2,500 Gm.

growth resembled carcinoma. Large groups of polyhedral cells formed solid alveoli or lay in several layers around an indefinite lumen. Between the alveoli were large groups of undifferentiated round cells. These rapidly dividing cells contributed the softness and the malignancy to the growth (fig. 7). At operation the capsule of the tumor tore, spilling blood stained serum, clots and small pieces of gray or pink neoplasmic growth. The tumor was almost diffluent, and was held

together with difficulty until it was hardened. On section round masses of brainlike consistency were present, and so were larger, softened areas infiltrated with recent hemorrhages. The kidney was much compressed at one pole of the mass. The 6 year old boy from whom this tumor was removed had a stormy postoperative convalescence, but was able to be about in two weeks. Within six weeks a recurrent mass was palpable, and he died about three months after operation

Operation was performed on seventeen of the eighteen children, and in one instance only was the tumor found inoperable. This also is in contrast to primary neoplasms in the suprarenal, which could not be removed by operation three times out of six. One child died before the operation was finished, another died of hemorrhage within a few hours, and one died on the fourth day. The others recovered from the operation and left the hospital in good condition. Four could not be traced. Three were known to be alive after ten months, six and three quarters years and thirty years. Two died at home within three or four months after discharge, and one after fifteen months, all with recurrent growths. Just as the primary growth may be insidious in its onset and not noted for months, so the recurrent tumor may be undetected in spite of careful examination only a few weeks before its obvious presence. Four patients died in the hospital, having been readmitted because secondary growths had occurred.

Necropsy was performed on five children, four showing locally recurrent growths from one to seven months after operation These were always situated at the site of the removed kidney and showed a tendency to spread over the entire abdomen. An especially rapid return was that which occurred in a child of 10 months. Enlargement of the abdomen was noticed two months after operation, a few weeks after he had been discharged from the hospital in good condition. The recurrent tumor grew rapidly and death took place after three weeks, when the abdominal circumference had become larger than it had been before operation. On the outer surface of this tumor small, round, soft masses were noted at operation, and they were also present on the pedicle. The growth had evidently broken through its capsule barrier, and the recurrence came from the cells of neoplasmic masses left on the pedicle The structure of the recurrent growth was not that of the original tumor. It differed in the absence of unstriped muscle cells. This rapidly recurring tumor was composed largely of the least differentiated type of cell, which expressed its rapid tendency to multiplication and its lawlessness in the softness and rapid extension of the original growth, as well as in the quick return and metastatic deposit in the liver The difference between the original and secondary growth is also of interest. A similar case

is noted by Wengraf,[9] in which a recurrent growth was devoid of the muscle and cartilage elements present in the primary tumor. In three other cases of this series the recurrent growths duplicated the structure of the primary neoplasm. The time between the removal of the primary growth and the appearance of a palpable, locally recurring tumor varied from one to thirteen months. Abbe [10] has reported a case in which a tumor appeared in the other kidney four and three quarters years after operation.

Metastases were found in three instances: in the lungs and liver once, in the lungs alone once and in the liver and lymph nodes once. The metastases in the lungs showed glomeruli, tubules and masses of undifferentiated cells. In one case unstriated muscle cells were absent, though present in the primary growth. Engelken [11] noted that the metastases were as complicated as the original growth. The neoplasms are transmitted through the blood stream. The regional lymph nodes were enlarged in one case, and then only slightly. This is another difference between kidney and suprarenal growths, which involve the lymph nodes early and extensively.

As to the origin of these renal neoplasms, it seems probable that they all come from the same type of embryonal cell, but that they come from that cell at different stages of its differentiation and consequently of its potency. The more embryonic and less differentiated the cells from which the tumor originates, the more complicated will its structure be, because of the multipotency of the undifferentiated mesodermal cell. Thus for the rhabdomyo-adenosarcomas it seems simple to presuppose a parent cell with an inherent ability to give rise to striated muscle, supporting tissues and kidney elements, since these are all mesodermal in origin and closely approximated in the young embryo, and the inclusion of such early cells within the developing kidney is possible. This was Wilms' [7] view. It seems the only way to account for the striated muscle tumors, for striated muscle cannot develop from unstriated muscle, and so metaplasia gives no adequate explanation of these growths. The presence of cartilage and bone in the mixed tumors is also explained. For the less complex tumors two possible origins suggest themselves. Either the parent cells are more differentiated, of later origin, and so have the potentiality only of the renal and supporting tissue elements, or the cells of the early renal blastema are adequate for the development of the tumors containing only kidney elements like tubules, connective

9. Wengraf, F.: Zur Kenntniss des sogenannten embryonalen Adenosarkom der Niere, Virchow's Arch. f. path. Anat. **214**:16, 1913.

10. Abbe, R.: Sarcoma of Kidney; Nephrectomy; Recurrence After Four Years and Nine Months in the Other Kidney, Ann. Surg. **25**:360, 1897.

11. Engelken, H., Jr.: Metastasierende embryonale Drüsengeschwülst der Nierengegend im Kindesalter, Beitr. z. path. Anat. u. z. allg. Pathol. **26**:320, 1899.

tissue and unstriated muscle. Again, growths with more embryonal epithelial elements may take their origin from an earlier cell of the renal blastema than that which gives rise to the more adenomatous forms, when the cells have reached the stage of differentiation of renal tubular epithelium. Since these neoplasms are not all alike, but only closely related, there seems no special reason why a single origin must be invoked for them as a group.

The spindle cell sarcoma would seem to come from mesodermal cells already incorporated in the renal blastema, either as part of its supporting framework or as an inclusion without definite work to do. In either case the cell had reached a period of development when its potentialities could go no further than the development of an embryonal connective tissue with no relation or resemblance to the structure of the organ in which it grew.

CLINICAL SYMPTOMS

There is a marked sameness about the history of these young patients. All were said to have been normal, full term infants, and to have gained normally. The first symptom noticed by the mother was enlargement of the abdomen, and for this relief was sought. Children who were old enough to walk when the abdominal enlargement became manifest usually walked less and with difficulty, though there was no acute pain or tenderness in any instance. The weight of the tumor alone was evidently sufficient to interfere with the child's free movements. At the same time loss of appetite and weight were noted in some of the cases Abdominal enlargement was not present at birth in any instance. As a rule relief for the abdominal enlargement or "lump in the side" was sought quickly, within from two to four weeks of its noticeable appearance. More rarely it was said to have been present for two or three months, and in the case of one infant, six months elapsed between the first appearance of the abdominal swelling and symptoms causing alarm. Abdominal enlargement was said to have been slow and gradual. In a boy, aged 2 years, none had been noted, and he was brought to the hospital for a digestive disturbance. Examination revealed the abdominal mass, and a fluctuating tumor weighing 345 Gm. was removed by operation. Death occurred about three months later.

The neoplasm usually occupied the entire side of the abdomen, from diaphragm to pelvic brim, and twice it extended beyond the median line. The swelling was firm, smooth and not tender. The liver and spleen were palpable and distinct from the tumor, and a piece of large intestine lay in front of it. Especially was this true of the sigmoid flexure when the growth was on the left side. The inguinal lymph nodes were enlarged in one case. In the others no glandular enlargements were found. Pain was either absent or not severe. Blood was passed in the

urine by three of the patients, and then it was noted but once and never continued over a long period. The invasion of the renal substance explained the symptom. Anemia and weakness were present in varying degree. Nevertheless, convalescence after operation was surprisingly rapid and uncomplicated in all but one case, the most malignant in the series.

The age at which the tumor was noticed varied from 2 months to 6 years, and the interval between the time it was noticed and the time of operation varied from three weeks to six months. Death occurred from three to fifteen months after the first symptom was noted.

SUMMARY

Eighteen primary renal neoplasms in children between the ages of 3¾ months and 6 years included one spindle cell sarcoma, thirteen adenosarcomas, three leiomyo-adenosarcomas and one rhabdomyo-adenosarcoma.

Embryonal renal neoplasms occurring in young children are a heterogenous group. They are closely related, but not identical histologically or histogenetically.

In all the tumors the kidney was sharply limited from the neoplasm by a capsule of compressed renal tissue. While the growth may invade the kidney substance, the fully developed kidney elements take no part in the new growth, which is entirely embryonal in type.

The more solid tumors are more easily removable, because they remain within their unbroken capsule. Four children who survived operation ten months or more had this firm type of tumor.

Metastases into the lungs and liver may develop from the firmer, as well as from the softer growths, but they appear less frequently and less early in the former type.

One patient survived to adult life, and one is well six years after operation. The growth was a rhabdomyo-adenosarcoma in the older girl, and in the younger an adenosarcoma showing more adenomatous than sarcomatous differentiation.

The prognosis in cases of primary renal neoplasms in young children is, therefore, not entirely hopeless.

METASTATIC CALCIFICATIONS IN THE ORGANS OF THE DOG AFTER INJECTIONS OF PARATHYROID EXTRACT *

WILHELM HUEPER, M.D.
CHICAGO

Deposits of lime salts in various organs occurring without previous degenerations in these organs are called "metastatic calcifications" (Virchow). Precipitations of calcium salts of this type are due either to an increase of the calcium in the blood or to a decrease of its solubility in the blood and the tissue fluids. The first mentioned condition is usually the result of extensive bone destruction as in osteomalacia, ostitis fibrosa, carcinosis and sarcomatosis of the bone, caries, etc. Experimentally it can be induced by intravenous injections of calcium salts, $Ca(C_3H_5O_3)_2$, $Ca_3(PO_4)_2$ (Tanaka,[1] Katase [2]). The other state may be caused by a decrease in the amount of albuminous substances in the blood as found during nephritis when considerable quantities of the blood albumin are excreted through the kidney-calcium gout (Schmidt [3]). The albuminous substances and the phosphates of the blood keep the calcium salts in solution and buffer greater changes in the p_H of the blood, preventing thereby the precipitation of the calcium. Calcium retention due to impaired kidney function, which was noted by Harbitz [4] as a causative factor, will be of little importance in this process, because only from 5 to 10 per cent of the total calcium excretion is done by the kidney, while the rest is removed by the large bowel. The organs most frequently affected are the lungs, the stomach and the kidneys. Their higher alkalinity compared with that of other organs and the blood accounts for this fact, because the calcium salts are less soluble in an alkaline than in an acid medium. The alkalinity of these organs is obtained by the continuous excretion of acids into their cavities leaving the tissue more alkaline.

In recent experiments with dogs performed by Dr. S. A. Matthews and Dr. Austin of the departments of pharmacology, physiology and

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1. Tanaka: Kalkresorption und Verkalkung, Biochem. Ztschr. **35**:111 and **38**:283, 1911.

2. Katase: Experimentelle Verkalkungen am gesunden Tiere, Beitr. z. path. Anat. u. z. allg. Pathol. **57**:516, 1914.

3. Schmidt, M. B.: Kalkmetastase und Kalkgicht, Deutsche med. Wchnschr. **34**:59, 1913.

4. Harbitz: Norsk. Mag. f. Laegevidensk. **78**:1129, 1917, quoted by Wells: Chemical Pathology, ed. 4, 1920, p. 443.

biochemistry, Loyola University,[5] investigating the calcium-magnesium relations in the body after injections of parathyroid extract, I had the opportunity to examine the organs of the animals for the effect of the hypercalcemia produced by the parathyroid hormone and found typical metastatic calcifications in many organs, in addition to other remarkable alterations. The clinical course observed in the animals receiving injections did not differ in general from the description given by Collip.[6] The time of onset and the strength of the symptoms were found to be dependent on the dose and the interval in which the injections of parathyroid extract were administered. In the beginning, when the blood calcium had exceeded the normal level by from 2 to 3 mg., a psychic depression, a slight decrease of the pulse rate and an increase of the urine excretion were observed. With increasing blood calcium the symptoms grew more urgent. The dogs began to vomit in attacks, especially after intake of fluid, the pulse rate dropped more markedly and became irregular. Simultaneously, the coagulation time showed a decrease from 2 minutes to 1½ minutes. In the final stage the animals vomited more freely a bloody mucoid material or even pure blood. Also, bloody stools were observed. The amount of the excreted urine was diminished or a complete anuria was present. The urine showed a slight turbidity after boiling (albumin +) and leukocytes and round kidney epithelial cells in the sediment. The dogs died after a period of general weakness and dizziness with the symptoms of coma. Necropsy was usually performed soon after death.

MACROSCOPIC ANATOMY

The vessels of the meningi and the brain were well filled with blood. There were no macroscopic hemorrhages. The thyroid gland was grayish yellow, firm, sometimes much harder than normal and of distinct follicular structure, with varying amounts of colloid. The lungs were grayish red and well distended. A foamy, serous fluid exuded from the cut surface and the bronchi. The pulmonary vessels were filled with dark red coagulated blood. The heart was firmly contracted and smaller than normal. The myocardium sometimes had a slight yellowish spotted appearance. The wall of the left ventricle was nearly twice as thick as normal and surrounded a narrow almost empty lumen.

The stomach was filled with dark red blood or coffee ground colored fluid, sometimes exceeding 1 quart in amount. The inner surface of the stomach was highly folded. The mucosa was markedly swollen and had a red jelly-like appearance. Smaller and larger hemorrhagic spots were not rare. These alterations were always restricted to the fundus part of the stomach while the pyloric region was sharply demarcated from the fundus by the lack of pathologic changes. Only small hemorrhages were occasionally observed; in general, the pyloric mucosa had a normal appearance.

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5. Matthews and Austin: The Effect of the Blood Calcium Level on the Tolerance to Magnesium; Some Observations on Hypercalcemia Induced by the Parathyroid Hormone, to be published.

6. Collip: The Parathyroid Glands, Medicine **5**:1, 1926.

The duodenum frequently showed the same red jelly-like swelling as the fundus of the stomach. It extended for about 20 cm. below the pylorus and was usually of a less degree than the same process in the stomach. In several cases multiple, round, shallow ulcerations were present in the mucosa, which were located on the anterior side of the duodenum, the uppermost about 10 cm. below the pylorus. The edges of the ulcers were sharp. Generally from six to eight of these penny-sized ulcerations were found.

The jejunum and the ileum were normal in all cases except for a certain degree of hyperemia and a bloody content in the lumen, being derived from the hemorrhage in the stomach and duodenum. The cecum and the colon were normal. The pancreas was firm, gray and well lobulated. The spleen was somewhat enlarged, dark red and moderately firm in consistency. The follicles were well visible on the cut surface. The liver was firm and dark brownish red. A quantity of dark red blood exuded from the vessels of the cut surface. A few of the smaller vessels in the interlobulary tissue contained red thrombi. The kidneys were firm in consistency, and grayish red with bluish red papilli. The suprarenal gland was normal. The genital organs were normal. In some cases the bladder was filled with a moderate amount of turbid urine; in other cases it was firmly contracted and empty.

MICROSCOPIC OBSERVATIONS

There were hyperemic vessels with frequent small perivascular hemorrhages in the region of the basal ganglions, pons cerebri and medulla oblongata. In one case, degenerative changes in the nervous substance adjacent to a somewhat larger hemorrhage with reactive accumulation of round cells was observed in the region of the basal ganglions.

Two types of thyroid glands were observed which differed in structure as well as in location of the calcium deposits. The one kind, resembling in architecture the normal human gland, was composed of regular round or oval shaped follicles lined by a cubical epithelium and filled with a red stained colloid, in which frequently dark bluish, coarse granules were present. In other follicles the colloid was stained diffusely dark blue as the result of a precipitation of calcium salts (fig. 1).

The structure of the other type was more similar to that of a human parenchymatous goiter. The follicles were somewhat irregular and lined by a high cubical or irregularly shaped epithelium which was sometimes desquamated and found in the lumen surrounded by a scanty, pale stained, filamentous colloid. The interstitial connective tissue was highly infiltrated with calcium salts and formed a dark blue stained framework in which the glandular formations were embedded (fig. 2).

The alveoli of the lungs were partly filled with a serous or serohemorrhagic fluid, mixed with desquamated alveolar epithelial cells. The capillaries in the alveolar septums were hyperemic. Calcium deposits were found in only a small number in the elastic membranes of the alveolar septums (fig. 3).

Leukocytic infiltrations were scattered throughout the whole myocardium. They were found either near small thrombotic vessels and capillaries or between and around the fragments of muscle cells. The muscle cells were frequently fragmented in wavelike streaks or in localized spots. A reactive leukocytic infiltration was not always present around these fragmentations but was usually lacking. The fragments had either straight or indented edges. Sometimes rests of the sarcolemma and hyaline granulated material were found

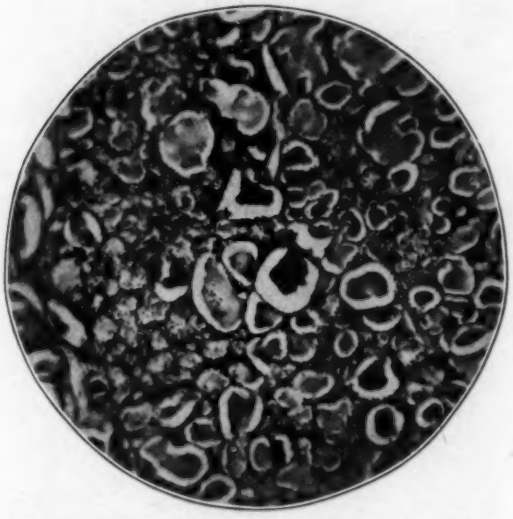

Fig. 1.—Calcium precipitates in the colloid of the thyroid gland.

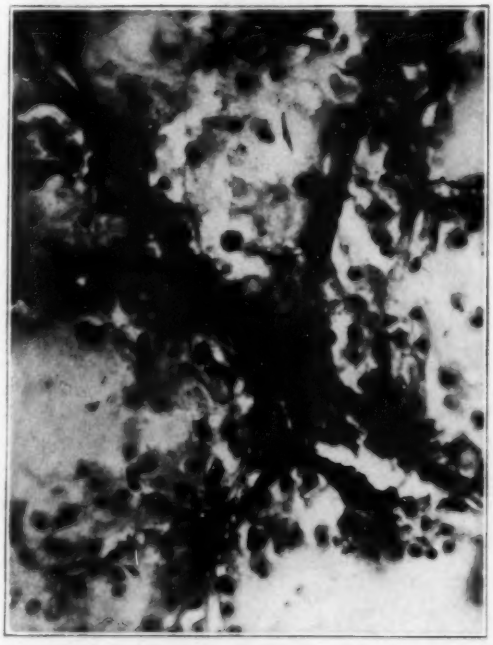

Fig. 2.—Calcification of the interstitial tissue of the thyroid gland.

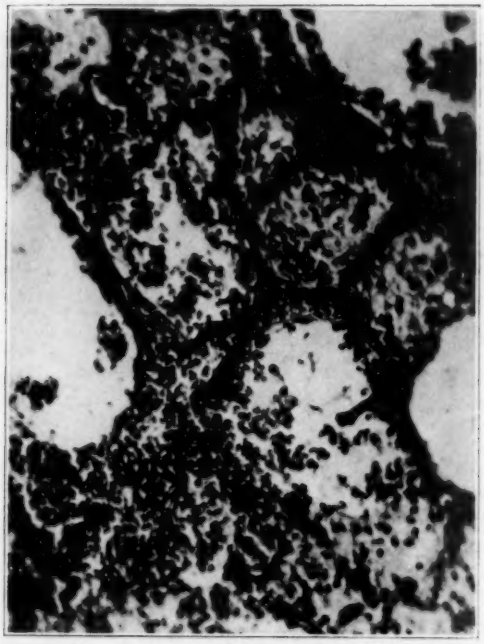

Fig. 3.—Calcium deposits in the elastic membranes of the alveolar septums of the lung.

Fig. 4.—Fragmentations of the heart muscle and leukocytic infiltrations.

between the fragments as signs of sarcolysis. Calcifications of single muscle cells were rarely seen (fig. 4).

In the fundus of the stomach the cylindrical cell lining of the mucosa was more or less completely necrotic and destroyed. A fibrinous layer containing some leukocytes covered the degenerated and also partly necrotic connective tissue framework of the mucosa. The cells of the fundus glands were also necrotic in the upper layers and showed signs of degeneration in the deeper parts of the mucosa. Calcified glandular cells were present in a large number (fig. 5). In the whole mucosa a diffuse hemorrhagic imbibition was present. The capillaries were filled to distention with blood, but ruptures of the wall were not observed in the deeper, better preserved parts of the mucosa. A diffuse leukocytic infiltration of the mucosa was seen in some cases. The

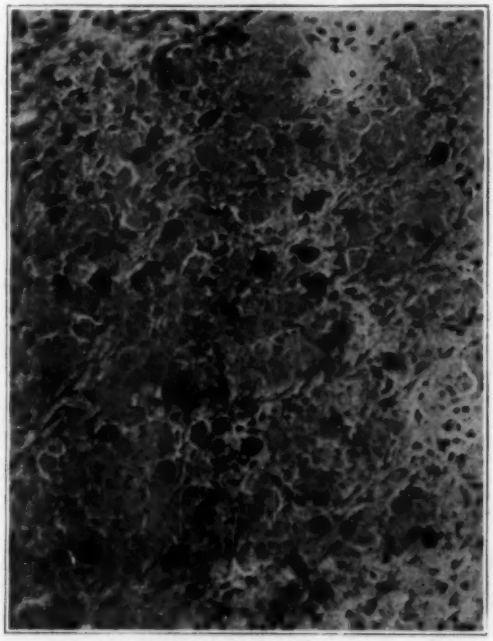

Fig. 5.—Calcified cells of the glands in the mucosa of the stomach.

vessels, especially the veins in the submucosa and subserosa were hyperemic and in some places thrombotic. In small arteries and veins the thrombi were sometimes formed by conglomerated leukocytes.

The microscopic observations in the pyloric part corresponded to the small macroscopic observations. The epithelial lining of the mucosa and the pyloric glands was in all cases well preserved, except for a few small superficial hemorrhages and epithelial defects which were surrounded by a reactive inflammatory zone. The capillaries and other vessels of the pyloric part were usually hyperemic.

On examination of the duodenum the cylindrical cell lining of the tips of the villi often was found to be lacking, and the stroma was covered by a fibrinous layer containing a few leukocytes. The villi were densely infiltrated with leukocytes, lymphocytes and plasma cells. The capillaries were dilated and hyperemic,

and hemorrhagic extravasations frequently were seen, but not of the same degree and to the same extent as those in the fundus of the stomach. In the ulcerated areas the cylindrical cell lining and the epithelium of the Brunner's glands were destroyed, and the defect was filled with a fibrinopurulent exudate. The ulcers never surpassed the muscularis mucosae. The vessels in the submusoca and the muscularis were hyperemic and also occasionally thrombotic. A high content of leukocytes was noticeable in the lumen of the vessels rather frequently. The muscle fibrils of the circular layer of the muscularis showed in some cases a localized, fine, grayish blue granulation due to the presence of precipitated calcium salts (fig. 6).

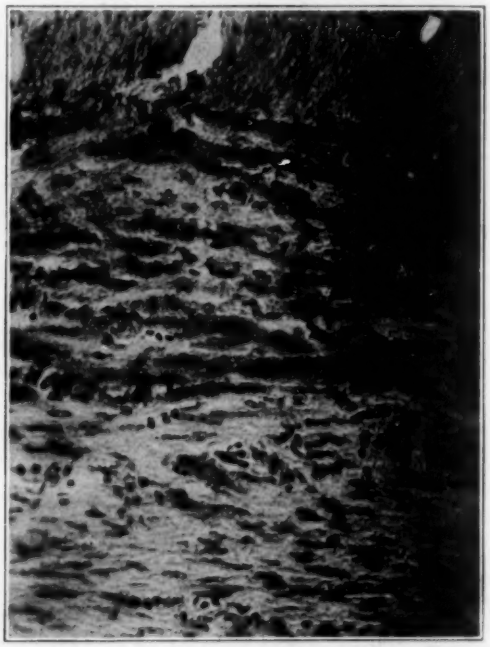

Fig. 6.—Calcium granules in the muscle cells of the circular layer of the duodenum.

Hyperemic vessels were found in the jejunum and the ileum.

The colon was normal.

In the pancreas the cells of the glands were degenerated in places. Necroses of small areas were also observed sometimes. The vessels were hyperemic, containing many leukocytes. Erythrocytes were found in some pancreatic ducts.

The spleen was hyperemic.

Degenerations and necroses of the liver cells were always present in some places. The process seemed to spread from the central vein. These alterations either involved wedge-shaped areas, or were diffusely scattered throughout the whole liver tissue, leaving well preserved only the liver cells in the periphery of the lobules, those along the interstitial septums and those underneath the capsule. The epithelium of the bile ducts and the interstitial connective tissue were usually without degenerative changes. The vessels were generally hyperemic, especially in the tissue adjacent to the anemic infarcts. The inter-

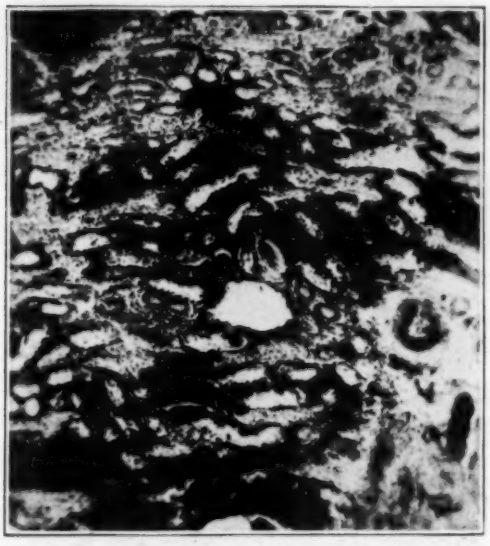

Fig. 7.—Calcification of the epithelium and the membranae propriae of the tubules of the kidney.

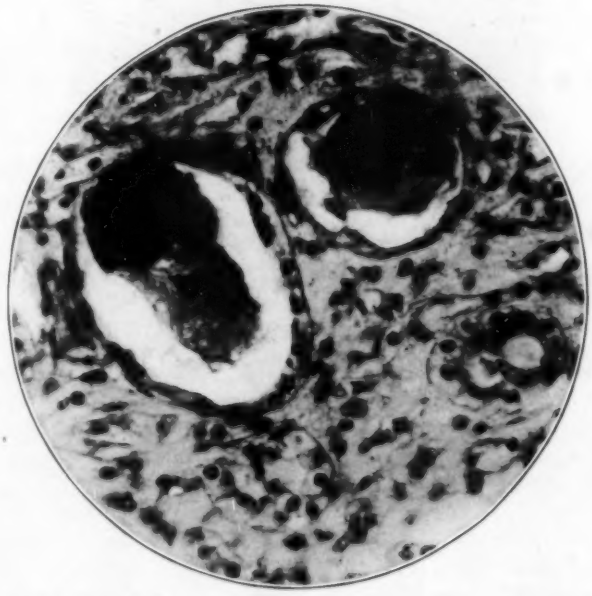

Fig. 8.—Calcium casts in the lumen of the tubules.

lobular branches of the portal vein were frequently thrombotic. A moderate diffuse leukocytic infiltration was present in the spaces between the columns of the liver cells. A generalized invasion of gram-negative rods into the liver tissue was observed in one case.

The capillaries in the glomeruli of the kidney were markedly hyperemic, and hemorrhages into Bowman's capsule space were seen occasionally. Serous exudation and desquamation of cells into the distended Bowman's capsule spaces were found more frequently. Degeneration and necrosis of the tubular epithelium was always present in a varying degree, appearing early in the course of the disease. Calcification of the tubular cells, sometimes extensive, was observed in all cases in which there was a hypercalcemia of about 20 mg.

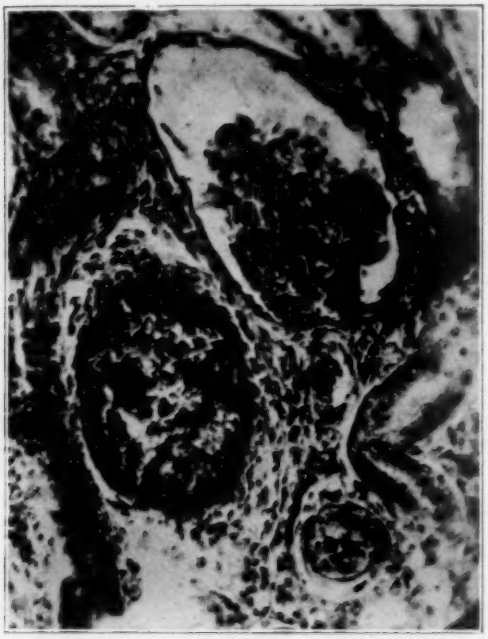

Fig. 9.—Calcium deposits in the wall of a small artery and of a Bowman's capsule.

In many instances the calcified cells were desquamated and conglomerated in the lumen, forming solid dark blue casts. In other tubules, especially in the collecting tubules, the epithelial lining was well preserved, but the lumen was filled with a material stained hyaline red in which dark blue coarse granules of calcium salts were present. Calcifications of the membranae propriae of the tubules and Bowman's capsules and of the elastic membranes of the arteries were frequently present. Small hemorrhages and round cell infiltrations were occasionally observed (figs. 7, 8 and 9).

In the suprarenal gland there was marked hyperemia of the medullary vessels.

The aorta was normal.

The skeleton muscle was normal.

COMMENT

The study of the causes and the correlations of the different pathologic alterations in the organs produced by overdoses of parathyroid extract must be based on the knowledge of the physiologic effects of this hormone. Regulating the calcium metabolism of the body, it controls the acid-base balance of the cells and body fluids and also the equilibrium in the tonus of the vegetative nervous system (parasympathetic nerve). The parathyroid extract given in physiologic doses induces: (1) a prolongation of the systole and shortening of the diastole of the heart; (2) a dilation of the vessels of the internal organs; (3) an intensification of the tonus of the stomach and intestine; (4) a rise in the calcium level of the blood.

The administration of excessive amounts of the parathyroid extract produces a pathologic exaggeration of the effects noted above. The diastole of the heart becomes gradually more and more incomplete, the pulse rate grows slow and irregular and the blood pressure drops considerably, impairing the general circulation. The dilation of the vessels of the internal organs is extreme. The excessive intensification of the tonus of the stomach and intestine causes vomiting and diarrhea. The highly increased blood calcium augments the coagulability of the blood and favors the formation of thrombi with secondary hemorrhages in the hyperemic organs. As a result of the oversaturation of the blood with lime salts, calcium precipitations are produced in important organs, eventually interfering with their proper functioning.

A critical consideration of the reported pathologic alterations, on the basis of the foregoing observations permits the following interpretations as to the causes and correlations.

The multiple hemorrhages in the brain are produced by stasis in the small veins and capillaries of the brain and represent secondary diapedetic extravasations. They were observed only in the brains of those dogs that died in coma, but were not seen in animals killed during an early stage of the hormone poisoning. The edema and the hyperemia of the lungs with secondary hemorrhages into the alveoli are also the result of the final breakdown of the circulation. The same cause is responsible for the thromboses in the interlobulary veins of the liver, an alteration which apparently takes place during the death agony, because almost no reactive leukocytic infiltration is found around the necrotic liver tissue. The localized necroses in the pancreas are probably caused by the activation of the pancreatic secretion in the ducts through the extravasated blood.

The process of the hemorrhagic imbibition of the mucosa of the stomach is somewhat more complicated. A disturbance of the circulation of the blood in the mucosa occurs in an early stage of the disease, caused by the prolonged and stronger contractions of the muscularis by

which the perforating veins are compressed. It results in a more or less marked passive hyperemia of the numerous small capillaries of the mucosa which possesses only scanty anastomoses. This condition is later aggravated by the effects of the general circulatory insufficiency, which leads to stases and thromboses in the larger vessels of the submucosa. At this stage the extravasations which appear with the increasing cyanosis in localized spots become diffuse, and finally involve the whole fundus of the stomach. Necrosis of considerable parts of the mucosa follows as a result of the hemorrhagic infarction. It is impossible to give a satisfactory explanation for the restriction of this process to the fundus of the stomach. It may be possible that a different p_H of the fundus mucosa compared with that of the pyloric part is responsible for this fact. But the occurrence of similar alterations in the duodenum does not favor this interpretation. It is noteworthy, however, that the hemorrhagic imbibition of the duodenal mucosa always appears later than the corresponding changes of the stomach, and never reaches the same degree.

Another important injurious effect of the parathyroid extract on the circulatory system is the occurrence of multiple small thrombi in the small vessels and capillaries of the myocardium. They lead either to small anemic necroses or to such injury of the muscle cell that fragmentation of the fibrils follows. These results are of interest so far as they substantiate the observations of Hektoen,[7] who was the only one to report the presence of leukocytic infiltrations around the fragmented muscle cells. He concluded from this observation that the fragmentation of the heart muscle may occur some time before death and is not always the result of agonal contractions (Kaufmann,[8] Stamer[9]) or of putrefactive processes after death (Aschoff,[10] Giese[9]). My results shows definitely that these changes may take place during life. The presence of darker and lighter stained portions of the muscle cells and the signs of sarcolysis of the fibrils are the results of hyperextension of the muscle.

Calcifications were found in the thyroid gland, the lungs, the heart muscle, the stomach, the duodenum and the kidneys. The occurrence of the calcium deposits in those organs which excrete or produce acids (lung, carbon dioxide; stomach, hydrochloric acid; kidney and heart, orthophosphoric acid) can easily be explained by their different reaction, being more alkaline than the blood. Calcium salts precipitate in these tissues, therefore, from the highly oversaturated calcium solution of the blood. But no explanation can be given as to the cause of calcium precipitates in the thyroid gland, and the relation of its structure to the

7. Hektoen: Segmentation and Fragmentation of the Myocardium, Am. J. M. Sc. **114**:555, 1897.

8. Kaufmann: Specielle Pathologische Anatomie, ed. 8, 1922, p. 1083.

9. Stamer: Untersuchungen über die Fragmentation und Segmentation des Herzmuskels, Beitr. z. path. Anat. u. allg. Pathol. **42**:310, 1907.

10. Aschoff: Pathologische Anatomie, ed. 4, 1919, p. 19.

localization of the calcium deposits. Differences apparently exist in the reaction of the interstitial tissue of the normal gland and the parenchymatous hyperplastic gland.

The calcifications evidently have no greater injurious effect on the function of the involved organs with the exception of those in the kidney. The gradually increasing calcification and destruction of the tubular epithelial cells, and the formation of calcium casts in the lumen of the tubuli blocking the drainage of the urine from the kidney, impair the kidney function more or less and induce a retention of phosphorus, ammonia and titrable acid (Collip) in the blood, with deleterious effect for the organism.

The increase of the acids in the blood resulting from this process is aggravated by the retention of carbon dioxide due to the circulatory insufficiency, the existing hyperphosphatemia and the loss of alkaline from the blood by the abundant hemorrhages in the stomach and duodenum and the severe vomiting. These factors work together to change the primary compensated acidosis into the final uncompensated, fatal acidosis.

The artificial introduction of the hormone of the parathyroid gland into the human body for therapeutic purposes is connected with certain dangers, and should not be done without a proper control of the blood calcium level to avoid alterations in the organs which may become definite, irreparable and fatal to the patient. An increase of the blood calcium to from 10 to 15 mg. over a longer period of time may be produced without greater risk for the patient. But the elevation of the blood calcium above this level will probably soon cause dangerous symptoms of the circulatory system, the stomach and the kidneys.

The material used in the foregoing experiments was purchased from a grant by the Committee on Scientific Research of the American Medical Association.

CONCLUSIONS

Metastatic calcifications in various organs were produced by the injection of overdoses of parathyroid extract.

The effect of the hormone on the action of the heart and the circulatory system is the cause of the hemorrhages, thromboses and secondary necroses in several organs.

The extreme degree of calcium precipitation in the kidneys leads to a considerable impairment of the function of these organs, which may become fatal to the organism.

The dangers connected with the therapeutic use of this hormone make a proper control of the blood calcium absolutely necessary.

EFFECTS OF INANITION ON THE STOMACH AND INTESTINES OF ALBINO RATS UNDERFED FROM BIRTH FOR VARIOUS PERIODS *

SHIRLEY P. MILLER, PH.D.
MINNEAPOLIS

Numerous observations have been made (chiefly by Jackson and Stewart) on the weight changes in the gastro-intestinal tract during periods of underfeeding in the albino rat, and similar studies have been made on other animals. The histologic changes during inanition have been less carefully studied, especially during the period of infancy. A thorough investigation of this problem seemed desirable, not only because of its general interest as a type of mammalian inanition, but also because of its special importance to human gastro-intestinal disorders. A brief summary of the results of this investigation was included in a report by Jackson.[1]

MATERIAL AND METHODS

One hundred and ten albino rats were used in the study. They are listed in two series. The first series comprised seventy-six rats. Fifty-three of these were test animals subjected to inanition by underfeeding from birth for various periods. Twenty-three were full fed controls. Thirteen of these controls were from the same litters as the test rats and were allowed to live until the last animal of the corresponding litter was killed. Such animals are designated as litter controls. Ten controls were taken from the stock cages of the colony. These are designated as weight controls, as they were of approximately the same body weight as the test rats at death.

The fifty-three test animals of the first series were chosen within twenty-four hours after birth, and were separated from the mother. They were returned to her at least once a day and allowed to nurse for a short time. The control animals from the same litter were allowed to remain continuously with the mother. The mother rats were fed with a standard normal diet used for the rat colony. In order to maintain a uniform degree of inanition the test animals were kept as nearly as possible at maintenance (constant body weight) for the maximum length of time. Some of the animals were able to secure more food than others and gained in weight. Such animals lived longer than those

* From the Institute of Anatomy, University of Minnesota.

1. Jackson, C. M.: The Effects of Inanition and Malnutrition Upon Growth and Structure, Philadelphia, P. Blakiston's Son & Co., 1925.

which were held slightly above or below the initial weight. In agreement with Aron,[2] Jackson [3] and Stewart,[4] it was found impossible to keep young rats alive for any extensive period, unless a slight increase in body weight was permitted. The test animals were killed in the last stages of starvation, or necropsy was performed immediately after death; but in no case were the animals used if rigor mortis was present, in order that postmortem changes might be avoided. The necropsy technic was similar to that employed by Jackson and Stewart. The weights of the liver, the spleen and in most cases the pancreas were also taken, as well as those of the alimentary canal. The stomach and intestines were weighed separately. Care was taken to prevent evaporation before and during weighing.

Regaud's neutral formalin Zenker fixing solution was used. The tissues were chromated according to Regaud's method. This permitted staining by the ordinary stains as well as by special stains. After fixation the tissues were embedded in paraffin and cut in sections two or three microns thick. Sections from each specimen were stained in one of the following: Delafield's hematoxylin and eosin; Unna's methylene blue and eosin; Altmann's aniline-water acid fuchsin, and counterstained with Mallory's connective tissue stain or with polychrome methylene blue; neutral gentian prepared according to Bensley.

The second series of rats comprised material used in a former study (Miller [5]) on the effects of inanition on the mitochondria. It included thirty-four albino rats older and larger than those used in the first series. Seventeen of these animals were allowed water only and were killed when in the last stages of inanition. The remaining seventeen were controls of the same age and of approximately the same body weight as the test rats. In this series no weights of the alimentary tract were taken.

The fixing solutions for this series were Bensley's osmic bichromate acetic and Regaud's neutral formalin Zenker. The staining was with Altmann's aniline-water acid fuschin stain, as modified by Bensley, and with Mallory's connective tissue stain.

An ordinary ocular micrometer was used in measuring the thickness of the coats of the stomach and the intestines. The measurements recorded are the averages from ten readings in each case unless other-

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2. Aron, H.: Nutrition and Growth, Philippine J. Sc., series B, **6**:1-51, 1911.

3. Jackson, C. M.: Changes in the Relative Weights of the Various Parts, Systems and Organs of Young Albino Rats Held at Constant Body Weight by Underfeeding for Various Periods, J. Exper. Zool. **19**:99-156, 1915.

4. Stewart, C. A.: Changes in the Relative Weights of Parts, Systems and Organs of the Young Albino Rats Underfed for Various Periods, J. Exper. Zool **25**:301-353, 1918.

5. Miller, S. P.: Effects of Various Types of Inanition Upon the Mitochondria in the Gastro-Intestinal Epithelium and in the Pancreas of the Albino Rat, Anat. Record **23**:205-210, 1922.

wise stated. The measurements of the cell diameters were made with a Leitz filar micrometer. A Zeiss 2 mm. apochromatic oil immersion lens with a compensating ocular was used. The measurements recorded are the averages from fifty readings in each case.

GROSS APPEARANCE AND WEIGHT CHANGES

Gross Appearance of the Body.—The bodies of the underfed rats are reduced in size when compared with the normal controls of the same litter. The hair in young rats is delayed in its appearance. It is shorter and rougher than that of the normal controls. The opening of the eyes is also delayed. The ears are white instead of normal pink. The skin appears tightly stretched over the feet and the tail, so that the bones are easily distinguished. This gives the tail a beaded appearance.

Gross Appearance of the Stomach.—In most cases the stomachs of the test rats contain food, even at death from inanition. At necropsy many stomachs are bloated with gas so that the walls of the cardiac portion appear transparent. Such stomachs may have a plug of undigested and curdled milk firmly packed in the pyloric opening. Other stomachs are quite flaccid, with only a small amount of bloody mucus in the pyloric region. The larger blood vessels appear congested as seen through the serosa.

The tunica mucosa of the cardiac region in the test rats appears normal and is glistening white. In the pyloric region this coat presents an abnormal, anemic appearance. By the use of a hand lens one may see numerous small ecchymoses distributed over the surface of the pyloric region. In many cases there are small ulcerated regions from 1 to 2 mm. in diameter.

Changes in the Weights of the Stomach.—For the study of the weight changes in the stomach, the data were secured from two sources. The weights of the stomachs of the controls and the test rats were observed directly. Weights of normal stomachs of the same body weight as each test rat were taken from the tables by Hatai.[6] As a check, the stomach weights of the controls were compared with the similar weights from Hatai's tables. There was only a small amount of variation, probably because of differences in the technic of weighing (fig. 1). The stomach weights from Hatai's tables were then used as a standard of comparison with those of the test rats of similar body weight. Two comparisons were made. The stomach weights of the normal rats from the tables and controls were made into a graph. To this graph were

6. Hatai, S.: On the Weight of the Epididymis, Pancreas, Stomach and of the Submaxillary Glands of the Albino Rat (Mus Norvegicus Albinus) According to Body Weight, Am. J. Anat. **24**:71-91, 1918.

added the individual stomach weights of the test rats (fig. 1). The stomach weights of the test rats were grouped according to body weight at death. The averages for these groups also were taken and compared with averages of similar groups of normal rats of the same average body weight.

In seven groups of test rats having an average body weight varying from 4.60 to 8.15 Gm., there were increases in the average weights of the empty stomachs from 51 to 149 per cent above the averages for normal rats of the same body weight. The test rats having an average body weight of 10 Gm. showed an increase of 133 per cent over the

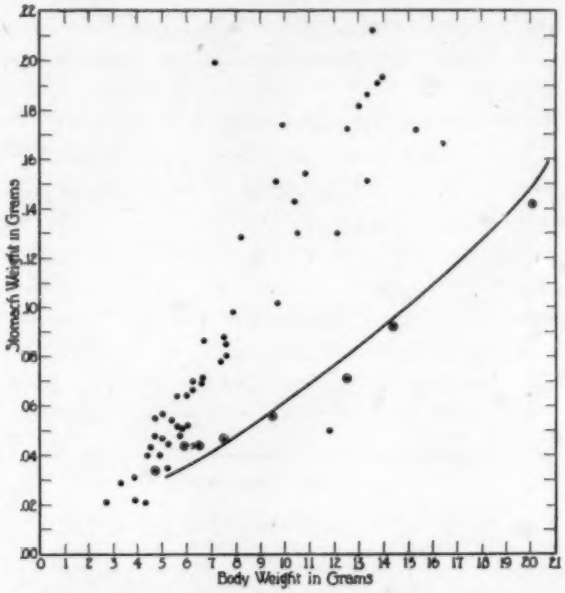

Fig. 1.—The relative weights of the stomach from the normal and the test rats; the normal curve is derived from the tables by Hatai; dots enclosed by circles are observed normal weights; solid dots are weights from test rats.

average weights of empty stomachs in normal rats of similar body weight. There was a similar increase of 102 per cent in the average empty stomach weight for the test rats having an average body weight of 13.9 Gm.

Gross Appearance of the Intestine.—The duodenum in the rats was often markedly congested, so that the wall appeared deep pink or even red. Usually it was partially filled with undigested milk, and occasionally it contains gas. The remainder of the small intestine in the test rats was deep orange or reddish brown. The color varied with amount of hemorrhage into the lumen of the intestine. In no case was the small intestine found entirely empty, even at death from starvation. In

approximately one half of the test rats the small intestine was dilated with gas. Often the distention was so great that the wall was thin and transparent.

The large intestine was usually pale pink. It was never completely empty and was often distended with gas. This was particularly noticeable in the case of the cecum. The blood vessels of the intestinal wall and of the mesentery often appeared congested.

Changes in the Weight of the Intestine.—The weights of the empty intestine of the test rats were taken without the mesentery and pancreas. The data for the normal weights of the stomach and the whole intestine were secured from Donaldson's tables.[7] The weights for the empty stomachs in the tables by Hatai [6] were subtracted from the total weights by Donaldson.[7] These data gave a series of weights for the normal

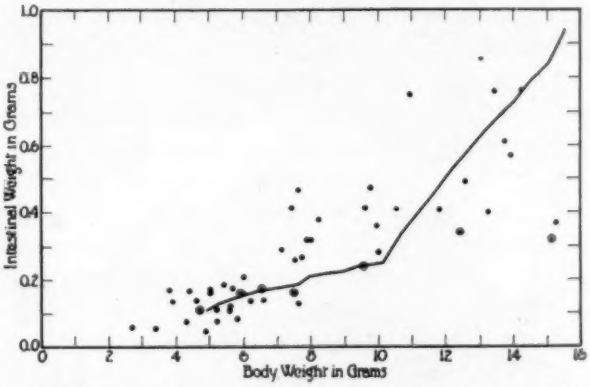

Fig. 2.—The relative weights of the intestine from the normal and the test rats; the normal curve is derived from tables by Donaldson and includes the weight of the pancreas and mesentery; dots with circle are observed weights of the normal intestine only; solid dots are observed weights of the intestine only from the test rats.

intestine including the pancreas and mesentery. My data do not include the weights of the latter structures, so it is possible to make only a relative comparison between the weights for the test rats and the normal data. The method of comparison is the same as that used for the stomach. The graph (fig. 2) gives the individual weights for the normal controls, and the normal curve derived from the tables by Donaldson and Hatai, with the individual weights of the intestines from the underfed test rats. The weights of the empty intestine were also arranged in groups according to body weight, and the averages of these were compared with similar averages for normal rats of the same

7. Donaldson, H. H.: The Rat, Memoirs of the Wistar Institute of Anatomy and Biology, ed. 2, no. 6, Philadelphia, Wistar Institute, 1924.

average body weights. In the groups with body weights of 4.60 and 5.38 Gm., the average weights for the intestine were 52 and 63 per cent above the averages of groups of normal rats of similar body weight. These results are in fair agreement with Stewart.[8]

The changes in the gastric and intestinal mucosa in my test rats resemble the descriptions by McCarrison [9] for adult pigeons and monkeys on diets deficient in various respects (vitamines, protein, salts, etc.). The small intestine of the rat was often greatly distended, but did not present the balloon-like expansions described by McCarrison for monkeys. The upper part of the colon was greatly distended in the test rats, as likewise found by McCarrison in monkeys. The pale color of the gastric mucosa and the frequent ecchymoses throughout the mucosa of the whole alimentary tract were observed by McCarrison. Similar atrophic changes in malnourished infants have been recorded by Baginsky,[10] Bloch,[11] Fischel [12] and others. The literature is fully reviewed by Jackson.[1]

The effects of inanition on the weights of the alimentary tract in rats have also been observed in a series of studies by Jackson and Stewart. Only a general comparison of their results is possible on account of different conditions involved. These differences include the age at which the animal was placed on the test, the character of the food and the severity of the inanition. Their data refer to the combined weight of the stomach and the intestine including the pancreas and mesentery, while mine are for the stomach and the intestine alone and separately.

HISTOLOGIC CHANGES

The changes in the histologic structure of the alimentary tract in the test rats include the structural changes of a regressive and atrophic nature and the changes in thickness of the various coats.

THE STOMACH

Tunica Mucosa.—The stomach in the rat is divided into two distinct parts. The cardiac or upper portion is lined with stratified squamous

8. Stewart, C. A.: Changes in the Weights of the Various Parts, Systems and Organs of the Young Albino Rats Kept at Birth Weight by Underfeeding for Various Periods, Am. J. Physiol. **48**:67-78, 1919.

9. McCarrison, R.: Studies in Deficiency Disease, Oxford Med. Publ., London, 1921.

10. Baginsky, A.: Die Verdauungskrankheiten der Kinder, Tubingen, 1884.

11. Bloch, C. E.: Untersuchungen über die Pädatrophie, Jahrb. f. Kinderh. **63**:421-445, 1906.

12. Fischel, R.: Diseases of Nutrition, in Pfaundler and Schlossman: Diseases of Children, Philadelphia, J. B. Lippincott Company, 1908, vol. 2, pp. 86-91.

epithelium. The pyloric or lower part contains the gastric glands and is covered with simple columnar epithelium. The stratified squamous epithelium forms a distinct fold or ridge separating the cardiac from the pyloric region. These divisions of the stomach and types of epithelial lining for the rat and allied species were described in the last century. A complete review of the literature is given by Oppel [13] in his comprehensive work on comparative histology.

The histologic changes in the cardiac portion during inanition are found chiefly in the stratified squamous epithelium. The intercellular spaces are more distinct than in normal tissue. These spaces are especially large in the stratum germinativum, in which they may be half the

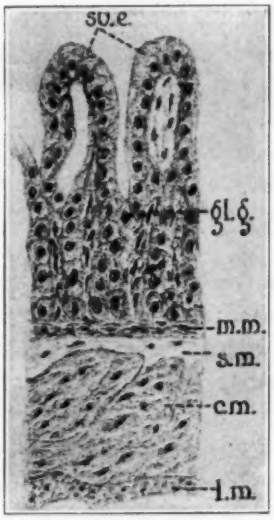

Fig. 3.—Section through the pyloric region of the stomach from a normal rat showing normal structure; body weight, 9.5 Gm.; age, 11 days. Magnification, 80 diameters; reduced one fourth; stain, hematoxylin and eosin. In this and figures 8 and 9: *c.m.* indicates lamina circularis; *gl.g.*, glandula gastrica; *l.m.*, lamina longitudinalis; *m.m.*, muscularis mucosae; *su.e.*, surface epithelium; *m.p.*, membrana propria; *s.m.*, submucosa.

width of the cell nuclei. The cytoplasm of these cells stains apparently normally, and there are no marked nuclear changes.

The normal gastric mucosa in the pyloric region of the albino rat resembles the descriptions of the same region in the mouse and other species of the rat, as reviewed in the work by Oppel. The normal surface epithelial cells have distinct boundaries and the cytoplasm is finely granular. Large mucous vacuoles lie near the free surface. The

13. Oppel, A.: Lehrbuch der vergleichenden mikroskopischen Anatomie der Wirbeltiere, Jena, Gustav Fischer, 1896, vol. 1-2.

chromatin is granular and uniformly distributed throughout the nucleus. The nuclear wall is distinct (fig. 3).

The surface epithelial cells in the test rats show various degrees of injury. In the rats underfed for the shorter periods the larger number of cells appear normal. Among these are cells with poorly defined borders. The cytoplasm stains faintly, the nuclear walls appear

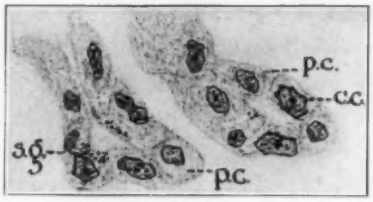

Fig. 4.—Section through the base of the gastric glands from a test rat; body weight, 7.6 Gm.; age, 34 days; cells shrunken; almost total absence of secretory granules—those present reduced in size; nuclei irregularly shrunken. Magnification, 870 diameters; reduced one fourth; stain, neutral gentian. In this and figures 5, 6 and 7: *c.c.* indicates chief cell; *c.a.*, canalicular apparatus; *mtr.*, mitochondria; *n.*, nucleus; *p.c.*, parietal cell; *s.g.*, secretory granules.

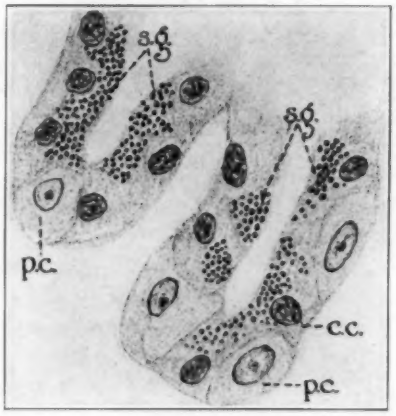

Fig. 5.—Section through the base of the gastric glands from the stomach of a normal rat; body weight, 9.2 Gm.; age, 43 days; chief cells show large numbers of secretory granules (*s.g.*); parietal cells apparently have no granules. Stain and magnification same as in figure 4.

irregular and the mucous vacuoles are reduced in size or may be absent altogether. Other cells show a coarsely reticulated cytoplasm, containing large nonmucous vacuoles. The nuclei are pyknotic or in various stages of karyorrhexis or karyolysis.

In the rats underfed for the longer periods there is an increased number of the injured cells, especially those showing the more pro-

nounced atrophic changes. However, there are always some cells which appear nearly normal. The cells lining the foveolae gastricae show similar injuries in varying degrees.

The gastric glands appear shrunken into the test rats. The amount of apparent shrinkage is greater in the rats underfed for the longer periods. The chief cells of the gastric glands appear somewhat smaller than those from the normal glands. Their cytoplasm stains poorly; the nuclei are pyknotic and stain faintly. In many cells the nuclei show stages of karyorrhexis or karyolysis. Specimens stained with neutral gentian show a reduced number and even an absence of secretory granules (fig. 4). Specimens from normal rats have these granules in large numbers (fig. 5). Paneth cells show a similar reduction of granules. The normal acid cells stained with acid fuchsin contain a large number of intensely staining cytoplasmic granules. These granules appear in groups with irregular branching spaces between them. Such

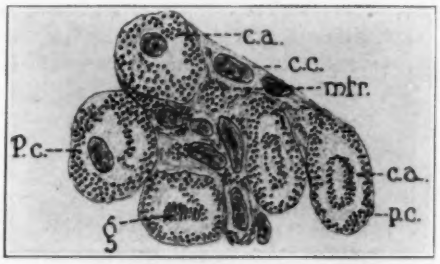

Fig. 6.—Section near the base of the gastric glands from the same normal rat as was used in fig. 5; showing granules in acid cells and canalicular apparatus. Stain, acid fuchsin and Mallory's connective tissue stain; magnification same as in fig. 5.

spaces are evidences of the canalicular apparatus (fig. 6). In the test rats the acid cells appear shrunken (fig. 7), and the canalicular apparatus is not visible. The granules appear to be reduced in number but they retain their brilliant staining reaction. Measurements of the acid cells show a decrease of from 19 to 37 per cent for the average lesser cell diameter in rats underfed for from fourteen to thirty-four days. The greater diameter is more variable.

In the areas of the gastric mucosa in which there were ecchymoses, the changes in the histologic structure are extreme. The surface cells are in most cases necrotic and form sheetlike masses of faintly staining disintegrating cells. These appear somewhat like a membrane on the surface of the mucosa (fig. 8). The gastric glands appear as strands of disintegrating and necrotic cells. The cell boundaries are difficult to determine and the nuclei show advanced stages of degeneration (fig. 8). The lamina propria in most of the test rats shows evidence of edema.

The edema is more pronounced in the rats underfed for the longer periods. The connective tissue cells appear somewhat shrunken. There is apparently no cell infiltration.

Tela Submucosa.—Structural changes in the tela submucosa are not well defined. In some instances there is apparently a slight edema. The blood vessels appear congested, but similar appearances are often observed in the normal rats. Occasionally the test rats show small hemorrhages in the submucosal spaces. Typical inflammatory conditions do not appear.

Tunica Muscularis.—The muscle cells show atrophic changes more frequently in the lamina circularis. Some of the muscle cells undergo a degeneration. The cytoplasm is at first granular, later it becomes clear and hyaline in appearance, while later it may be filled with connective tissue.

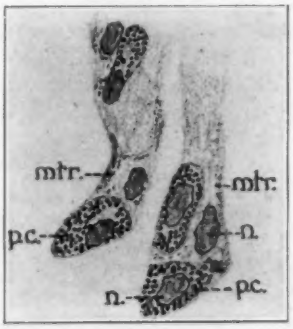

Fig. 7.—Section through the base of the gastric gland from the same test rat as was used in fig. 4; showing shrunken cells and the absence of canalicular apparatus; granules in parietal cells remain brilliantly stained. Stain and magnification as in fig. 4.

Changes in Thickness.—In spite of the regressive and atrophic changes in the tunica mucosa of the test rats, this layer continues to grow in thickness (figs. 3 and 9). The stratified squamous epithelium of the cardiac region is increased 53 per cent in thickness in a group of test rats having an average body weight of 9.66 Gm. (comparisons being with normal rats of similar body weight). The epithelial ridge separating the cardiac from the pyloric region in the same groups likewise shows an increase of 69 per cent in thickness. There is also a continued growth in the height of the gastric glands in the test rats. In some of the test animals the height of the glands is twice that in normal rats of the same body weight. In a group of test rats with an average body weight of 7.78 Gm. the average height of the gastric glands is 71 per cent greater than the normal.

Measurements of the submucosa in both the normal and the test rats are too variable to draw conclusions. Measurements of the tunica

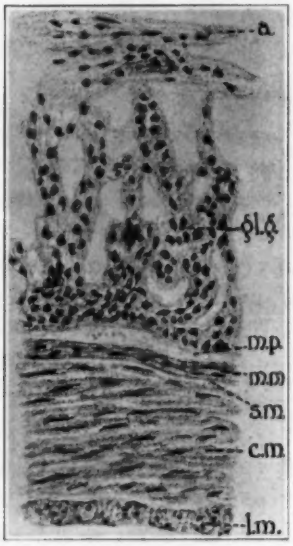

Fig. 8.—Section through the atrophic area from the pyloric region of the stomach from a test rat; body weight, 7.6 Gm.; showing atrophic tunica mucosa: *a* indicates necrotic epithelium; *m.p.*, edema in membrana propria; degenerating nuclei of the gastric gland may be seen. Magnification, 80 diameters; reduced one fourth.

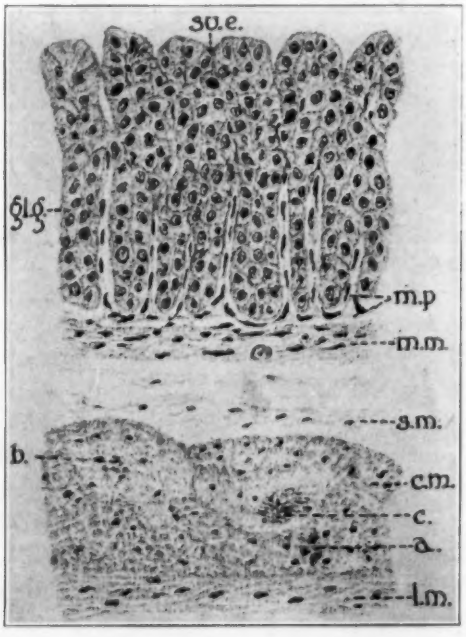

Fig. 9.—Section through the pyloric region of the stomach from a test rat; body weight, 9.66 Gm.; showing shrunken nuclei in the surface epithelium and gastric glands; slight edema in the membrana propria at the base of the gastric glands; and an area of degeneration in the tunica muscularis: *a* indicates swollen cells; *b*, irregular shrunken cells; *c*, complete degeneration. Magnification, 80 diameters; reduced one fourth; stain, hematoxylin and eosin.

muscularis show a decrease of 30 per cent in the thickness of the lamina circularis in the test rats. The thickness of the lamina longitudinalis was so variable for both the normal and the test rats that conclusions are not justified.

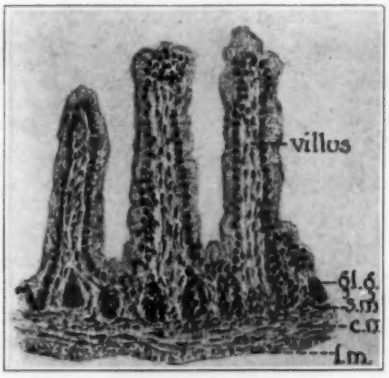

Fig. 10.—Section through the duodenum from a normal rat; body weight, 6.5 Gm.; age, 2 days; showing normal villi, glands of Lieberkühn and the various tunics. Stain, hematoxylin and eosin; magnification, 80 diameters; reduced one fourth. In this and the following figures: *c.m.*, indicates lamina circularis; *gl.l.*, gland of Lieberkühn; *m.p.*, membrane propria; *l.m.*, lamina longitudinalis; *s.m.*, tela submucosa; *su.e.*, surface epithelium.

Fig. 11.—Section through the duodenum from a test rat; body weight, 7.6 Gm.; age, 34 days; showing degenerated epithelium and villi in the lumen, shrunken glands of Lieberkühn, and other tunics with retarded growth; comparison should be made with fig. 10. Stain, hematoxylin and eosin; magnification, 80 diameters; reduced one fourth.

SMALL INTESTINE

Tunica Mucosa.—The epithelial cells of the small intestine exhibit similar changes of varying intensity. In many of the test rats the villi are in part or totally disintegrated. The lumen of the intestine is often filled with masses of degenerated cells (comparison should be

made with figs. 10 and 11). The glands of Lieberkühn appear shrunken, with atrophic cells. The cytoplasm stains poorly. The cell boundaries are difficult to determine. The nuclei show pyknosis and stages of karyorrhexis or karyolysis. When stained with neutral gentian, the Paneth cells in these glands show the granules decreased or absent. There appears to be a small amount of edema in the lamina propria, but no cell infiltration.

Tunica Submucosa.—This layer does not show well defined edema. There are no evidences of inflammation.

Tunica Muscularis.—Atrophy of the muscle cells is not as well defined as in the stomach.

LARGE INTESTINE

Tunica Mucosa.—In the test rats, changes are less evident in the tunica mucosa of the large intestine than in that of the small intestine

Fig. 12.—Section of the large intestine from a normal rat; body weight, 12.5 Gm.; age, 10 days; showing normal structure. Stain, hematoxylin and eosin; magnification, 80 diameters; reduced one fourth.

or the stomach. The surface epithelium shows but slight changes in its faintly staining cytoplasm. The cell boundaries are somewhat less clearly defined than in the normal, and the nuclei present slightly irregular walls. The glands appear somewhat shrunken. Their cells show various degrees of injury. There is a variable amount of edema in the lamina propria (comparison should be made with figs. 12 and 13).

Tunica Submucosa.—The edema is usually slight in this tunic as in case of the stomach and the small intestine of the test rats. Occasionally there are hemorrhages of the small submucosal vessels apparently.

Tunica Muscularis.—This coat likewise showed but little change in the test rats. No atrophy of the muscle cells was observed.

Changes in the Thickness.—Changes in the thickness of the coats of both the small and the large intestine are apparently also less than in the

stomach. Measurements of the tunica mucosa of the small intestine were unsatisfactory because of the degeneration of the villi. Those for the tunica submucosa were variable and inconclusive. The lamina circularis of the tunica muscularis is somewhat reduced in thickness in the test rats. The lamina longitudinalis apparently does not decrease in thickness. No measurements were made for the large intestine. However, there is an increased growth of the tunica mucosa, similar to that in the stomach.

Histologic changes somewhat similar to those described for the test rats are recorded by McCarrison [9] for adult pigeons, guinea-pigs and monkeys dying from various deficiencies in the diet. In many cases the

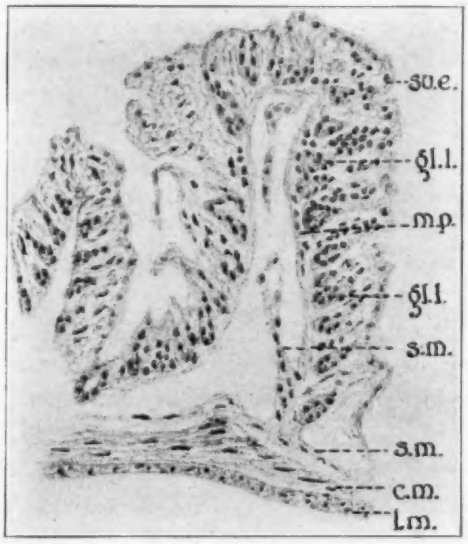

Fig. 13.—Section of the large intestine from a test rat; body weight, 13 Gm.; age, 43 days; showing continued growth of the mucosa, edema in membrane propria, shrunken glands of Lieberkühn and abnormal nuclei; comparison should be made with fig. 12. Stain, hematoxylin and eosin; magnification, 80 diameters; reduced one fourth.

epithelium was largely necrotic, as in the extreme atrophic regions of the gastric mucosa in my test rats. Capillary hemorrhages in the gastric mucosa were frequently noted by McCarrison. Gastric hemorrhages (ecchymoses) were likewise found in my test rats, and also occurred in the small intestine. McCarrison describes edema in the lamina propria, which likewise occurred in my test animals. However, I did not observe the edema which he describes in the tunica muscularis in the vicinity of Auerbach's or Meissner's plexuses. The atrophy of the gastric tunica muscularis was apparently greater in McCarrison's animals than in mine.

Parrot,[14] Fischel,[12] Schelble [15] and Aschoff [16] give descriptions of variable changes in the gastric tunics in malnourished human infants.

The changes from the normal in the structure of the small and the large intestine in my test rats are also similar in many respects to those described for other types of inanition. Shrinkage and degeneration of the villi in starved puppies was described by Quattrochi.[17] The descriptions by McCarrison for test animals fed on various inadequate diets correspond in general to those given for my test rats. The literature on this topic is comprehensively reviewed by Jackson.[1]

SUMMARY

1. In albino rats severely underfed from birth for various periods of time (to forty-three days), the weights of the empty stomach and intestine were much greater than in normal (younger) rats of similar body weight. The increase in the weight of the stomach appeared relatively much greater than that of the intestine.

2. In comparison with younger controls of similar body weight, there also appeared in the test rats a marked absolute increase in the thickness of the gastric tunica mucosa. This in part accounted for the increase in gastric weight. There was, however, a decrease in the thickness of the tunica muscularis.

3. Histologic preparations also showed a variable amount of edema in the lamina propria of the gastric mucosa in the test rats. The edema was more severe in the rats underfed for the longer periods of time, and also might in part account for the increased gastric weight. Stomachs with the most marked edema showed the greatest apparent increase in weight.

4. In spite of the increased growth in the weight and thickness, the gastric mucosa in the test rats showed regressive structural changes to a variable extent. These changes included atrophy and degeneration in restricted areas of the surface epithelium. The cells showed nuclear degeneration and cytoplasmic changes, including vacuolization and loss of secretory granules. In extreme inanition the tunica mucosa became almost completely necrotic in some instances.

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14. Parrot, J.: Des maladies des enfants; athrepsie, France méd. **21**:515, 1874.

15. Schelble, H.: Bakteriologische und pathologisch-anatomische Studien bei Ernährungsstörungen der Säuglinge, Leipzig, Georg Thieme, 1910.

16. Aschoff, Ludwig: Pathologische Anatomie, ed. 15, Leipzig, Johann Ambrosius Barth, 1921, vol. 1, p. 752-753.

17. Quattrochi, S.: Alterazione del tubo gastroenterico di cagnolini resi atrofici per insufficiente, cattira, o irregolare alimentazione, Pediatria **9**:49-67, 1901.

5. Distinct changes from the normal structure were not apparent in the gastric tela submucosa, except for occasional hemorrhages from the submucosal vessels.

6. The gastric tunica muscularis in the test rats showed a variable degree of atrophy and degeneration in the muscle cells. The degeneration did not involve the whole thickness of the tunica but occurred in restricted regions. In some places the muscle cells completely disappeared and were replaced by fibrous connective tissue.

7. In the small intestine of the test rats the villi appeared variably atrophic and in extreme cases were completely disintegrated.

8. The intestinal glands of Lieberkühn likewise appeared atrophic and decreased in size, with degenerative nuclear and cytoplasmic changes.

9. The lamina propria in the small intestine of the test rats showed edema which doubtless, as in the stomach, was a factor in causing the increase in weight.

10. The tunica muscularis of the small intestine in the test rats did not present such marked atrophy of the muscle cells as that which appeared in the stomach.

11. The large intestine in the test rats showed changes in general similar to those observed in the stomach. The tunica mucosa increased in thickness. Regressive changes of the surface epithelium and of the glands of Lieberkühn were observed. There was edema in the lamina propria and to a slight extent in the submucosa. Definite atrophy in the muscle cells in the tunica muscularis was not observed, however.

12. The histologic changes observed in the test rats during the present chronic underfeeding experiments resembled more or less those described by other investigators in the alimentary tract of various animals subjected to different types of total or partial inanition. They also somewhat resembled those described for atrophic infants, but appeared in general more pronounced, and less variable.

THE STRUCTURE OF INFECTIOUS SPLENIC SWELLING

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BROOKLYN

Splenic swelling is one of the most common lesions in infectious diseases. In spite of its importance as a diagnostic sign, little is known about the nature and histogenesis of the process.

To quote MacCallum's [1] textbook, it has been recognized that further work is required to make clear the complex nature of acute splenic swelling, which in some cases seems to be a response to the presence of the débris of red corpuscles or other cells, and in others, to the diffusion of toxin or bacteria.

Evans [2] has carried out a study on the forms of acute splenic swelling in human beings and those produced experimentally in animals. He confirms the sharp distinction made by MacCallum and others between the red types found in typhoid fever and the gray in pyogenic infections. As to the gross appearance, Evans states that the red type is softer and often diffluent. The capsule of the acute red spleen is always tense. the acute gray spleen is also soft but not diffluent, and it maintains its shape. Its capsule is often not tense but never wrinkled.

Kaufmann [3] gives a somewhat different description. From his experience Evans' description applied well to the typhoid spleen while the other type is most commonly found in pneumonia, typhus, septicemia, plague and other infectious diseases. In pyemia, however, the spleen is mostly soft and diffluent. The same might be found in scarlet fever, while in diphtheria the enlargement of the follicles is the outstanding feature.

My own experience which I have gathered from a large number of necropsies, which comprise a proportionately large number of infectious cases, coincides more with the opinion of Kaufmann.

I believe that acute splenic swelling can be classified in five groups. The first would comprise the typhoid spleen (MacCallum, Evans). The second is the gray type seen by the same authors, which is most commonly found in pneumonia and other acute infections. The third would comprise Kaufmann's pyemic type which is most commonly encountered in puerperal infections or in severe types of septic endocarditis, as well as in any acute septic condition which lasts longer than about a week.

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1. MacCallum: Textbook of Pathology, Philadelphia, W. B. Saunders, Company, 1925, p. 527.
2. Evans: Bull. Johns Hopkins Hosp. **27**:356, 1916.
3. Kaufmann: Lehrbuch der spezielle pathologischen Anat., 1922, p. 164.

The fourth should comprise those cases which are marked by extreme hemorrhages. They are most frequently encountered in epidemics of influenza and typhus fever, although the hemorrhagic spleen, like any other hemorrhage, is not absolutely characteristic of either typhus or influenza, and it is most probably due to some complicating infections with pyogenic micro-organisms. The fifth group eventually would include those spleens which show few changes in the pulp while the enlargement of the follicles is most conspicuous. The most typical example of this group is the diphtheritic spleen; similar spleens, however, are frequently found in other infectious conditions in childhood.

It is frequently observed that there is an increase in the size of the spleen with the continuation of the infectious process. The softness of the spleen in those cases is less apparent, so that what I have been in the habit of calling subacute splenic swelling is often quite firm, and the pulp cannot be scraped off of the section. In chronic infectious conditions the large spleen is tough and reveals a smooth cut surface with visibly thickened trabeculae.

The gross features of the infectious spleen suggest the following questions: 1. What is the cause of the enlargement in acute splenic swelling, and does the cause differ from that of the chronic enlargement? 2. Why is the former soft and of a variable consistency, while the latter is uniformly firm? 3. What is the meaning of splenic enlargement in infectious diseases?

It is generally believed that a chronic splenic swelling owes its firm consistency to connective tissue formation, while the acute splenic swelling is soft as a consequence of prevailing cellular infiltration. It has been claimed that hyperemia is chiefly responsible for both swelling and softness of the acute splenic enlargement. This is disproved by the cases of cardiovalvular disease or polycythemia in which extreme hyperemia is present but the spleen shows increased firmness.

The character of the cellular infiltration was poorly understood in consequence of the complicated structure of the normal spleen. Since the oxydase reaction and the methods of vital staining came into use, there has been more knowledge concerning the cellular content of normal and pathologic spleens.

Besides the lymphocytes which build up the splenic follicles and form sheaths around the blood vessels, the most important cells of the spleen are the reticulo-endothelial cells. These form the lining of the splenic sinuses and the cellular meshwork of the pulp between the sinuses. In between the reticulum are found the polymorphonuclears, myelocytes and other myelopotent mononuclear cells, together with plasma cells and oxydase negative mononuclears. It is understood that red blood cells and occasionally nucleated red cells belong to the cellular stock of the spleen pulp.

A detailed description of the acute red type in typhoid cases has been given by Mallory. He found the smaller vessels and splenic blood spaces filled with large phagocytic cells which he said were derived from the proliferation and desquamation of the endothelial cells lining the spaces. The proliferation was emphasized by the presence of some mitosis. These large phagocytes which contain mostly red cells and other cellular débris soon degenerate and become bound together by a meshwork of fibrin. In the pulp a number of plasma cells were encountered, while the polymorphonuclears were conspicuously absent.

Evans, while confirming Mallory's observations of the red type, described the gray type as showing few if any changes of the reticulo-endothelial cells. Those which line the sinuses neither are swollen nor show proliferation. The reticulum cells proper may reveal some swelling, but their number is not increased; they do not show any proliferation to speak of and phagocytosis is not a common observation.

Typhoid infection in rabbits produces changes similar to those in human beings in from three to seventy-two hours, although it seems that the number of plasma cells is less, whereas cellular necrosis is conspicuous. Infections with pyogenic cocci increased the number of myelic oxydase positive cells enormously in from five to fifty-four hours. No swelling or proliferation of the reticulo-endothelium has been noticed. "These cells," says Evans, "might perhaps assume phagocytic activities, but such activities are not conspicuous and altogether neglectable in comparison to those of the leucocytic cells."

Evans completed his experiments by poisoning rabbits with benzene and destroying the leukocytes. In these animals poisoned by benzene only the red type of acute splenic swelling could be obtained, regardless of the nature of the infectious agent. The splenic swelling of the animals poisoned with benzene was apparently much smaller than that of the controls.

I have undertaken to analyze the histogenesis of infectious splenic swellings and have continued this work, which I began abroad years ago, on postmortem material from New York City Hospital and United Israel-Zion Hospital, Brooklyn. In this paper I shall give a brief survey of the results. A series of papers to follow will deal with experimental research along the same lines.

COMPOSITION OF SPLENIC TISSUE

The splenic tissue is composed of: erythrocytes, myeloid cells, lymphocytes, plasma cells and reticulo-endothelial cells.

Erythrocytes.—The number of erythrocytes varies greatly. In some cases the venous capillaries and sinuses of the pulp are engorged with little blood; in other cases erythrocytes are scattered throughout the pulp, mixing freely with the other cells without any apparent capillary

or reticulum injury. Such diffuse hyperemia is usually well distinguishable from hemorrhage which causes manifest destruction of the splenic tissue or at least pushes the reticulum elements visibly apart. However, it is not always possible to decide whether some erythrocytes have extravasated or are still within the limits of the splenic circulation. The erythrocytes have a double pathway in splenic circulation; they may go from the capillaries to the sinuses and then leave the spleen with the venous outflow; or they may evade the sinuses altogether and travel through the meshes of the reticulum, as has been shown by Weidenreich. Erythrocytes following the latter path may infiltrate the reticulum to an extent which simulates hemorrhagic infiltration. Extreme softening of the spleen, which includes as one of its main features the dissociation of the reticulum cells, after the splenic fibrillar system and part of the reticulum has been broken up, might bring about conditions which are similar to those of hemorrhagic infiltration.

Phagocytosis of erythrocytes is a most common feature in infectious splenic swelling. The extent of phagocytosis, however, varies considerably, and so does the amount of hematogenous pigment. The process of red cell phagocytosis which takes place in the reticulum cells, and to a lesser extent in the sinus endothelium, is well known.

Myeloid Cells.—Polymorphonuclear leukocytes, myelocytes and nongranular but oxydase positive mononuclear cells belong to the normal cellular constituents of the pulp of the spleen. Whether these cells were retained in the spleen from the circulating blood or were autochthonous cells of the spleen was a matter of considerable discussion. To discuss the histogenesis of these cells is beyond the scope of this paper. It suffices to say that ripe leukocytes may gather in the spleen from the circulating blood, but others are certainly formed in the spleen from native myelopotent cells, which do not come from, and do not migrate into, the circulating blood (Paramusoff [4]).

An increase in the number of oxydase positive cells in the splenic pulp is encountered in acute splenic swelling of recent origin. The exact time of their appearance is less likely to be determined from human material. It seems, however, that they belong to the early stage of splenic tumor only and disappear gradually if the infectious disease is of somewhat longer duration. In the pyemic cases of the embolic or thrombophlebitic type, with infarcts or extensive necrosis, the leukocytic aggregation persists and may lead to abscess formation. In subacute splenic swelling their number is usually markedly decreased, and in the chronic forms they are hardly more numerous than in normal spleens.

Lymphocytes.—Lymphocytes form the bulk of the malpighian follicles and are scattered among the pulp elements. The appearance of

4. Paramusoff: Folia haemat. **12**:195, 1911.

the follicles does not always change in acute splenic swelling, although the lymphocytes are often somewhat larger in cytoplasm, and the presence of cells resembling lymphoblasts seems to indicate an increased proliferation. Many of these larger cells within the follicles, however, should not be classed with lymphoblasts. These large, round or polyhedral cells with a much lighter staining nucleus of the endothelial type usually occupy the central area of the follicle and have been spoken of as the "germinative center." Similar cells are scattered throughout the whole lymphatic apparatus of the spleen and can be demonstrated as

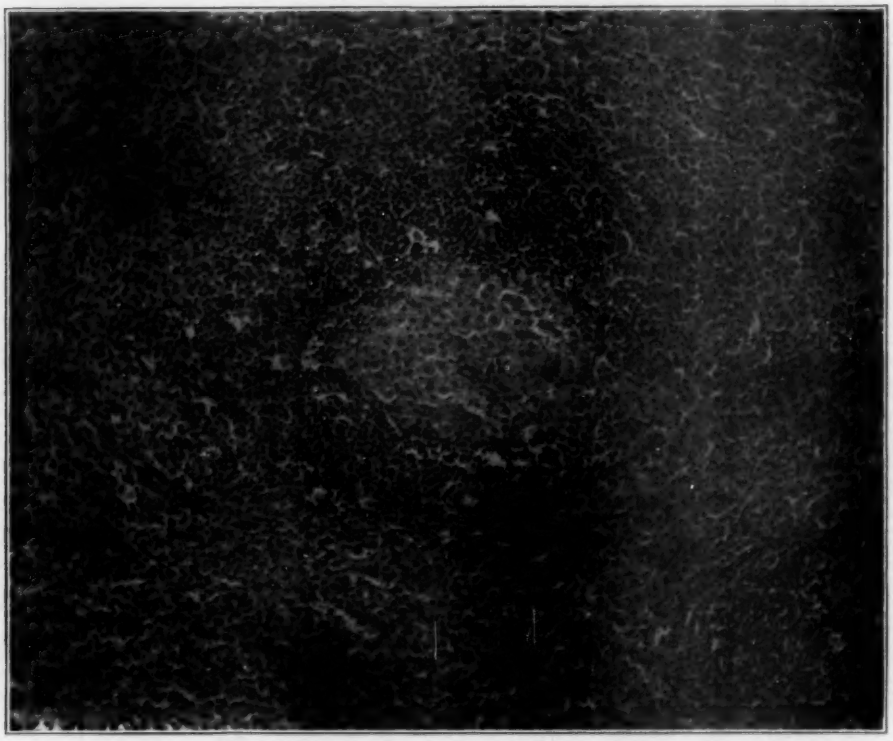

Fig. 1.—Perforated appendicitis; acute splenic tumor; central macrophage hyperplasia of the follicle. Leitz apochromatic lens, 16 mm.

belonging to the reticulum. All these cells are eager phagocytes and contain cellular débris, particularly nuclear fragments but no erythrocytes. They differ functionally also from the rest of the splenic reticulum as they do not take up vital dyes readily.

It has been claimed that bulky foci of such large "lymphoid" cells are characteristic of diphtheric infection. Although their prevalence in human as well as in experimental diphtheria cannot be contested, it is fair to say that they are certainly not pathognomonic for diphtheria

(MacCallum). I have observed them in various other infectious diseases, most frequently in typhoid, paratyphoid and scarlet fever, but also in other nonspecific infections. Figure 1 demonstrates such a pseudogerminative center in a case of acute peritonitis.

The common feature in reticulo-endothelial hyperplasia of the follicles is the youth of the patients. This also explains why such observations have been most regularly associated with diphtheria.

Reticulo-Endothelial Cells.—Any examination of the reticulo-endothelial cells in the spleen ought to include the reticulum cells proper, the

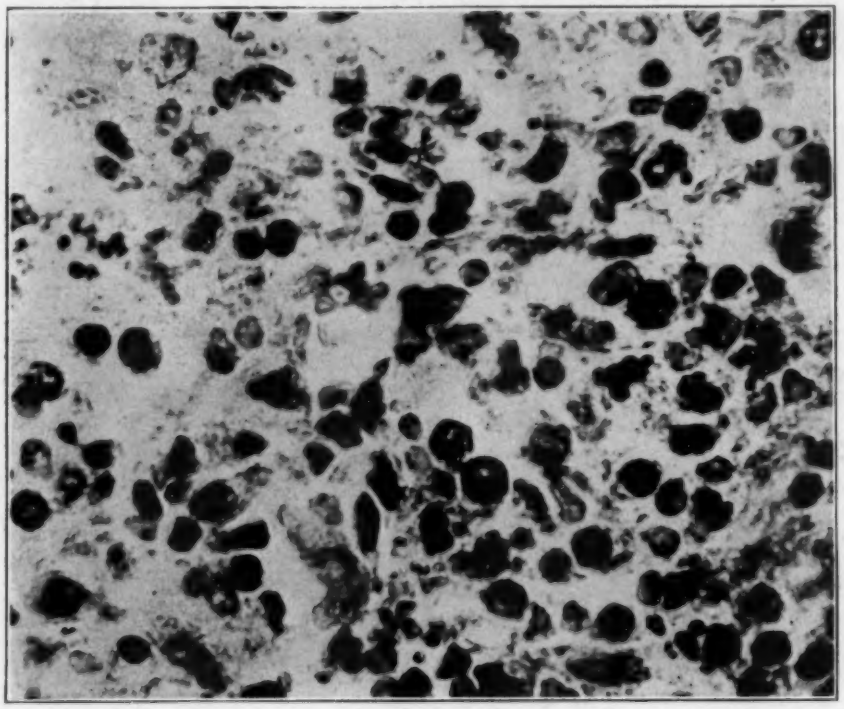

Fig. 2.—Puerperal sepsis and acute splenic tumor in a woman, aged 26; chromatolysis of the reticulum cells; swelling and chromatolysis of the endothelium of the sinus. Leitz apochromatic lens, 4 mm.

sinus endothelia and eventually the intercellular substance. The latter, if examined with Bielschowsky-Maresch's silver impregnation method, yields an elaborate meshwork of fibrils ("Gitterfasern"), which are most likely direct offsprings of the protoplasmic reticulum. These fibrils form heavy bundles within the splenic collagenous stroma, in the trabeculae and about the larger vessels. They furthermore follow the smallest capillaries and are seen in the wall of the splenic sinuses as the only interstitial substance to support the endothelium. The fibrils of

the sinus walls are much thinner than those of the capillaries; still thinner are these fibrils in the reticulum which often cannot be distinguished sharply from protoplasmic intercellular processes.

The essential observations in acute splenic swelling are those on the reticulo-endothelial system, in contradistinction to Evans' statement. The first reaction of these cells is that of chromatolysis, or of rhexis. Such cellular necrosis leads to the disappearance of the cells, although many cell shadows and nuclear débris still indicate the fate which befell the reticular histocytes. It is not so easy to find these cell shadows and

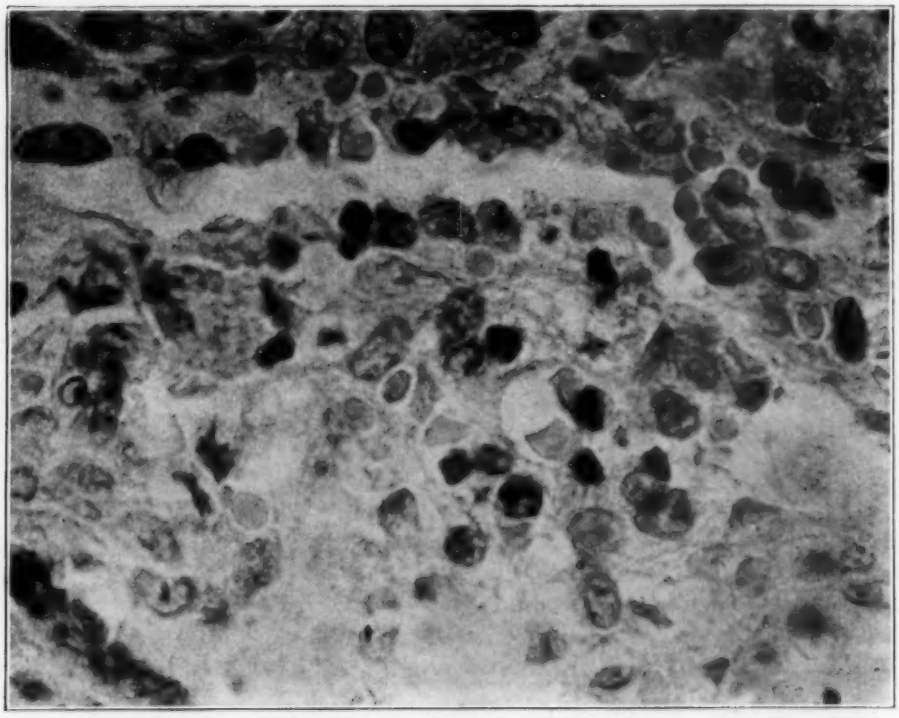

Fig. 3.—Puerperal sepsis and acute splenic tumor in a woman, aged 23; chromatolysis and desquamation of the lining cells of the sinus; Leitz apochromatic lens, 2 mm.

connect them to the reticulum cells, particularly if the pulp engorges with polymorphonuclears. Even more difficult is the observation of these early forms in the sinuses, as the injured endothelial cells are rapidly cast off. Figure 2 demonstrates reticular chromatolysis, while figure 3 demonstrates the same process on the lining cells of a sinus.

Along with the chromatolysis of the reticulum cells the cytoplasm is also injured and the reticulum breaks up more or less extensively. The softer the spleen the fewer fibrils are demonstrable by silver impregna-

tion (fig. 4). Further study must reveal whether they are all broken up or their disappearance is due to inability to stain. At any rate, it seems that the friability and softness of acute infectious spleens is consequent to the injury of the reticulum fibrils and varies with the degree of their lesion.

Already, in an early stage of the acute splenic swelling, proliferation of the reticulo-endothelial cells can be seen. This applies not only to the red type, as described by Mallory and corroborated by Evans, but to all the other types as well, although the degree of proliferation may vary substantially. It seems, however, that the variance of proliferation is by

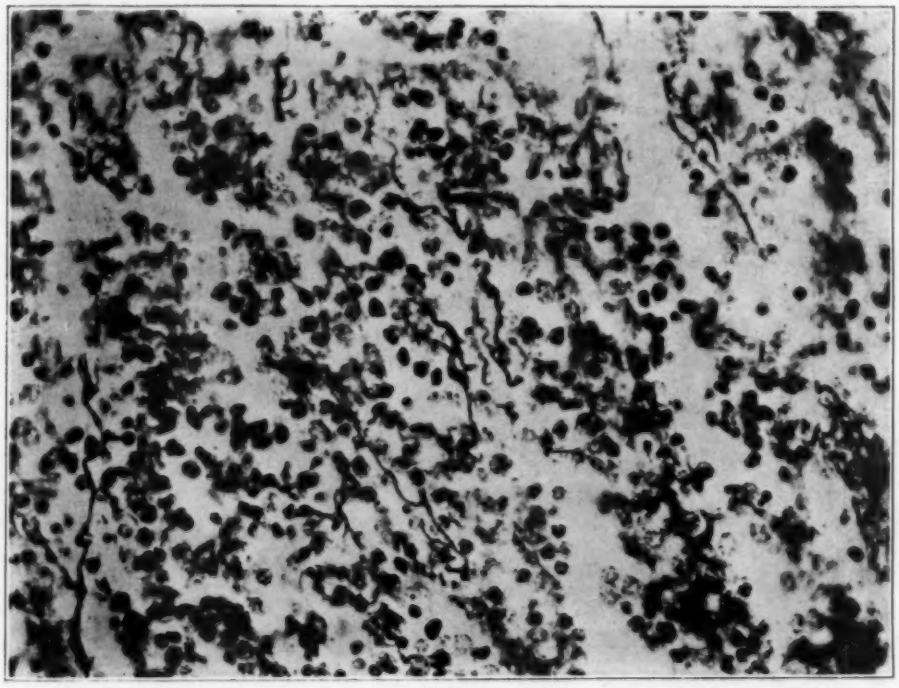

Fig. 4.—Pyemia, osteomyelitis; acute splenic tumor; fibrils broken up; finer fibrils disappeared, beginning dissociation. Gitterfasern, Bielschowsky-Maresch method; Leitz apochromatic lens, 4 mm.

no means due to the infectious agent. It rather seems that the more toxic the infection and the shorter therefore its duration, the less the extent of the proliferation. Close examination of the sinus endothelium reveals in almost every case of acute splenic swelling a definite regenerative proliferation (fig. 5). This is most marked in sinuses which have been denuded of their linings by chromatolysis or desquamation.

In the reticulum the early proliferation is less apparent although probably just as extensive as in the sinuses. Another sign of reaction is

the appearance of large cells with definitely basophilic cytoplasm which do not differ morphologically or tinctorially from plasma cells. The difference is in the nucleus only, which is much larger than the lymphocytic plasma cell nucleus and does not show the characteristic wheel-spoke structure. The nuclei are often large, round or oval, and most of them contain one or two hyperchromatic nucleoli.

These large basophilic cells are seen in both the reticulum and the sinuses. While it is impossible to determine the genesis of these cells from the reticulum cells, it is comparatively easy to find sinuses showing the process of developing basophilia of some lining endothelial cells. However, soon after the development of the cytoplasmic basophilia the cells desquamate and are found detached in the lumen of the sinus.

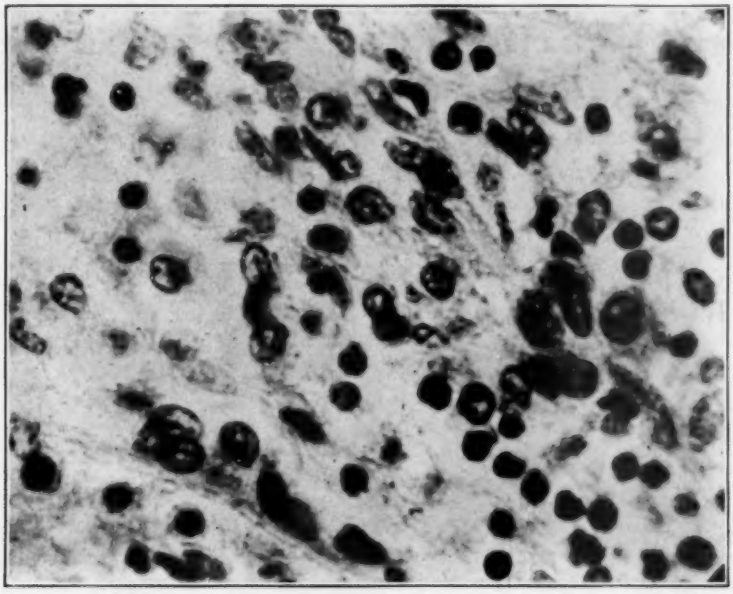

Fig. 5.—Septic pyemia and acute splenic tumor in an infant, aged 2 weeks; proliferation of the endothelium of the sinus. Leitz apochromatic lens, 4 mm.

The reticulo-endothelial basophilic cells may be seen in the earliest stages of acute splenic swelling, but they seem to be more numerous when the course of the infection continues.

It is impossible to decide whether the plasma cells which have been described in typhoid spleens by Mallory, Evans and others and those observed in different infectious splenic swelling by Huebschmann [5] include the cells which I have mentioned above, but I think this is most probable. Plasma cells are, of course, common in any kind of infectious

5. Huebschmann: Verhandl. d. deutsch. Path. Gesellsch. **16**:10, 1913.

splenic swelling. However, the cells which I have described above are morphologically and histogenetically altogether different, although they may express a similar biologic process.

Early in the infectious process, there is a distinct proliferation of the reticulo-endothelial cells. This is easier to observe in the sinuses than in the reticulum. While some of the endothelial cells are cast off and others reveal various stages of chromatolysis, some of the remaining cells probably proliferate by amitotic division, since the lining of such sinuses shows marked irregularities and puckering, and may even duplicate occasionally (fig. 6). The longer the infectious process lasts, the more marked is the endothelial proliferation within the sinuses.

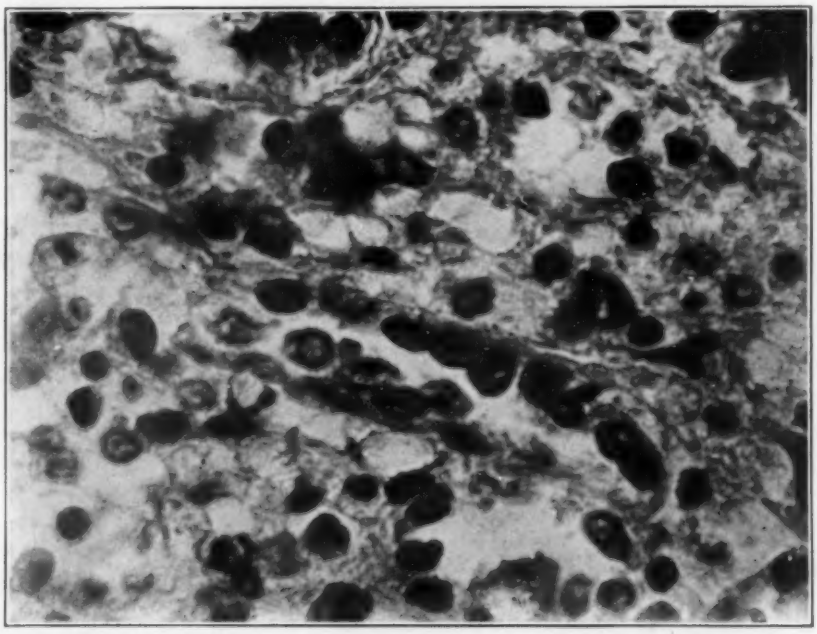

Fig. 6.—Recurrent endocarditis; acute splenic tumor; marked proliferation of the endothelium of the sinus. Leitz apochromatic lens, 4 mm.

New sinus formation could not be demonstrated directly. Nevertheless, the large increase in the size of subacute infectious spleens, in which the sinuses do not show any decrease of density, indicates that the formation of new sinuses is proportionate to the intumescence of the spleen. In view of the large size of such subacute splenic swellings, the amount of newly formed reticulo-endothelial cells is most remarkable.

In chronic infection the hyperplasia of the reticulo-endothelial system is also considerable, although the density of sinuses may decrease along with the cellularity of the reticulum. In such chronic cases a fairly dense fibrillar meshwork is formed in the reticulum containing but few

fibroblasts, the fibrils of which do not show the regular tinctorial features of common collagenous tissue. Silver impregnation shows that the reticulum fibrils are hyperplastic. It seems, however, that the whole increase in interstitial substance is not composed exclusively of such fibrils.

The lesser density of sinuses in some of the chronic splenic swelling is not due to an increase of the stroma only. Another reason is the peculiar distention of the sinuses which may remind one occasionally of a cavernous angioma (fig. 7). Such distended sinuses apparently are

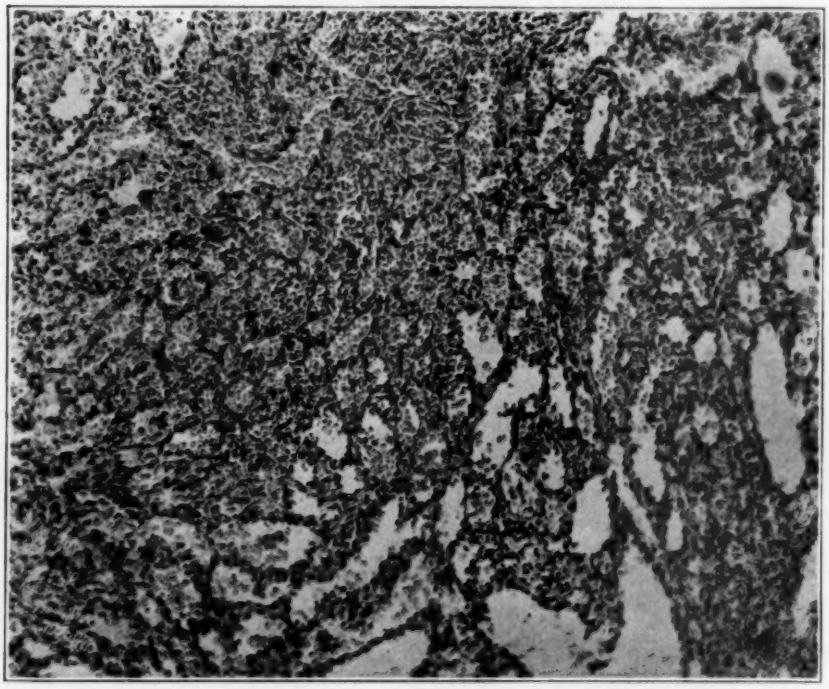

Fig. 7.—Perisplenitis, perihepatitis, distended sinuses mostly empty; acute splenic tumor. Leitz apochromatic lens, 16 mm.

not due merely to passive congestion, as they are often found empty. The gross appearance of such spleens is equally not that of a congested spleen. The most marked examples of such sinus changes are found in liver cirrhosis, and such spleens are often pale. Therefore, the distention of the sinuses must be attributed to some shrinkage in the splenic stroma or reticulum rather than to any inside pressure.

COMMENT

The description indicates that the main feature of splenic participation in infectious processes is that revealed by the reticulo-endothelial system.

This consists mainly in an early injury to these cells, which is presented by extensive lysis or rhexis of the nuclei and the casting off of endothelial cells of the sinus Soon, however, a proliferation of the remaining uninjured cells sets in which not only substitutes for the lost ones but by over-regeneration exceeds by far the original number. Hence, one of the main causes for splenic enlargement in infection is the proliferation of the reticulo-endothelial cells within their old boundaries as well as in newly built up spleen tissue. The latter prevails in subacute and chronic cases.

The injury to the reticulo-endothelial cells also includes that of the reticulum fibrils which are an integral part of that system The breaking up of the protoplasmatic reticulum and particularly of its fibrils reduces the resistance of the splenic tissue against both outside pressure and that of circulating blood and lymph This explains the softening of the spleen in the acute splenic swelling and the frequency of blood and plasma extravasations in the splenic pulp which increase the size of the organ and add to the dissociation of the pulp elements

The regenerative processes of the reticulo-endothelial system include also that of the fibrils Therefore, in splenic swelling of longer duration much less softening might be observed, and in subacute cases the consistency of the spleen is well increased Such a process leads to a more or less extensive induration of the splenic pulp which is, however, altogether different from simple fibrosis as seen after the healing of infarcts or other extensive necrosis.

The nature of the infectious agent also bears certain influence on the tissue changes. Bacterial infections, as with typhoid bacillus, which bring about leukopenia, are responsible for the absence of myeloid cells. Other infections are accompanied by greatly varying myeloid cell formation which may be so heavy as to hide the changes of the reticulo-endothelium in the beginning.

It is important to emphasize the leading rôle of the reticulo-endothelial changes, because this leads to a proper understanding of the splenic swelling It was known long ago that the reticulo-endothelial cells are phagocytes and take up cellular débris Splenic swelling has even been explained as a waste basket which takes up all the remainders of blood cells destroyed in the circulation (Jawein,[6] Bernhardt[7]). These cells, however, are much more than mere scavengers, nor is their function exhausted by the storage of iron and fat substances. There is strong evidence that the reticulo-endothelial system, a most important part

6. Jawein: Virchows Arch. f. path. Anat. **161**:461, 1900.
7. Bernhardt: Beitr. z. path. Anat. u. z. allg. Pathol. **55**:35, 1913.

of which is located in the spleen, leads in the defense mechanism against infections and partakes in the production of antibodies. This has been demonstrated by Gay and Clark,[8] Rosenthal and Spitzer,[9] Oeller,[10] Paschkis,[11] Siegmund,[12] Bieling and Isaac,[13] Neufeld and Meyer [14] and others.

Splenectomy seems to decrease the formation of antibodies, and much fewer antibodies are formed in animals in which the reticulo-endothelial system has been blocked by vital staining. In immunized animals there is a larger amount of agglutinins in the blood of the splenic vein than in venous blood obtained from the ear (Rautmann [15]). Splenectomy in rats lessens their natural resistance so much that they succumb to an endogenous infection—the so-called pernicious anemia of rats. Such anemia does not occur spontaneously and is encountered only after splenectomy. However, the disease is easily transmittable to other animals by the inoculation of liver emulsions (Lauda [16]). I want to refer eventually to the apparently beneficial effect of splenic organotherapy on experimental tuberculosis, for the animals on which opotherapy was used survived the controls for a considerable time (Bayle [17]).

It would be beyond the scope of this paper to enumerate all the manifold evidence which points toward the spleen as being the main factor in the processes of immunity and resistance. Morphologic observations like those which are reported here give the same indications. Apparently the reticulo-endothelial apparatus is particularly sensitive to bacterial and also to other possible toxins Such toxins may injure or even kill some of these cells, while all which survive respond with the production of antibodies and the increase of the cellular defense processes. They also respond with proliferation, replacing the lost elements and adding an excess of new tissue which participates in the defense activities. Therefore, the splenic swelling in infectious diseases must be looked on as a useful manifestation of the defense mechanism and ranks among those which suggest a teleologic interpretation.

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8. Gay, F. P., and Clark, A. R.: Reticulo-Endothelial System in Relation to Antibody Formation, J. A. M. A. **83**:1296 (Oct. 25) 1924.
9. Rosenthal and Spitzer: Ztschr. f. Immunitätsforsch. u. exper. Therap. **40**:529, 1924.
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12. Siegmund: Klin. Wchnschr. **1**:2556, 1922.
13. Bieling and Isaac: Ztschr. f. d. ges. exper. Med. **28**:180, 1922.
14. Neufeld and Meyer: Ztschr. f. Hyg. u. Infectionskrankh. **42**:594, 1924.
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SUMMARY

A review of the histology of the spleen in infections suggests a classification into five types: the hyperemic, the septic, the pyemic, the hemorrhagic and the lymphatic types.

Early in infection there is an injury to the reticulo-endothelial cells of the spleen consisting of chromatolysis and a breaking up of the reticulum which is rapidly followed by regenerative cellular proliferation, greatly in excess of the primary injury. The injury to the reticular stroma accounts for the softening, and its regenerative hyperplasia explains the increased consistency and chronic swelling.

Splenic swelling is interpreted as a useful manifestation of defensive mechanism against infections.

ALEUKEMIC MYELOSIS *

R. H. JAFFÉ, M.D.
CHICAGO

The existence of an aleukemic form of myelogenous leukemia has long been considered doubtful. In the earlier literature on this disease, much confusion is encountered, because different names were used for the same condition. Weil and Clerc,[1] and Vaquez and Aubertin,[2] spoke of an anemia with myeloid splenomegaly, which they though was different from leukemia. Later, Aubertin and Menétrier referred to a "leucemie myeloide." In other publications, the name "leukanemia" is found (von Leube, Parker Weber [3]). Donhauser [4] described a case of hematoplastic splenomegaly with sclerosis of the bone marrow, belonging to the same group.

A clearer conception of what sometimes was also called "myeloid pseudoleukaemia" was gained from Hirschfeld's [5] studies. He used the term "aleucemic myelosis," which was more correct than pseudoleukemia. Hirschfeld's publications were followed by the reports of a large number of cases (Berblinger,[6] Chosrogeff,[7] Goia,[8] Frank,[9] Hannema,[10] Keuper,[11] Kohn,[12] Kraus,[13] Naegeli,[14] Levy,[15] Schwarz,[16]

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* From the Department of Pathology, University of Illinois College of Medicine, and the Uihlein Memorial Laboratory of the Grant Hospital.

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4. Donhauser, J. L.: The Human Spleen as an Haematoplastic Organ, as Exemplified in a Case of Splenomegaly with Sclerosis of the Bone Marrow, J. Exper. Med. **10**:559, 1908.

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6. Berblinger: Verhandl. d. deutsch. path. Gesellsch. **21**:375, 1926.

7. Chosrogeff, cited by Naegeli.

8. Goia, S.: Un cas de myelose aleucemique aboutissont par l'evolution a la myelose leucemique, Arch. d. mal. du coeur, **19**:167, 1926.

9. Frank: Aleukaemische Myelose, Klin. Wchnschr. **1**:298, 1922.

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11. Keuper: Ueber die Diagnose der aleukaemischen Myelose, Deutsches Arch. f. klin. Med. **130**:118, 1919.

Szilard,[17] Weinberg,[18] and others). In selecting these cases, sufficient criticism has not always been employed, so that the clinical and hematologic picture threatens to become confused again.

In some of these cases, observations of the blood did not warrant the diagnosis of aleukemic myelosis, which was based merely on the total number of white cells. Normal or subnormal leukocyte counts in typical myelogenous leukemia are far from rare. Remissions occur, as they do in pernicious anemia, either spontaneously or induced by therapeutic measures, such as irradiation of the spleen. In the acute forms, low values of leukocytes are common (Gulland,[19] King,[20] Kohn, Kwasniewski and Henning,[21] Richter,[22] Weinberg, and many others). The differential count is the deciding factor. If a larger percentage of myelocytes, or even myoblasts, are found, the adjective "aleukemic" should not be added to the diagnosis of leukemia, although the total number of white cells may amount to less than 6,000. The number of the cells is not as significant as the degree of their maturity. Myeloid leukemia or leukemic myelosis is sufficient to characterize this disease. If it is desired to express in the name the low total number of leukocytes, such terms as "aleukocythemic" (Waterhouse,[23] King) are preferred.

If the name aleukemic myelosis is restricted to those cases in which the blood picture shows no evidence of an excessive proliferation of the blood-forming tissue, the cases published by Chosrogeff (39 per cent myeloblasts), Frank (12 per cent myelocytes), Kohn (up to 80 per cent myeloblasts), Kraus (20 per cent myelocytes and from 4 to 11 per cent myeloblasts), Levy (from 9 to 11 per cent myelocytes), Szilard

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12. Kohn, F.: Ueber einen Fall akuter Mikromyeloblastenleukaemie mit aleukaemischen Blutbefund, Ztschr. f. klin. Med. **96**:513, 1923.

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23. Waterhouse, cited by King.

(first case, 23 per cent myelocytes and 4 per cent myeloblasts; second case, myelocytes up to 30 per cent and myeloblasts from 37 to 49 per cent) and Weinberg (from 19 to 46 per cent myeloblasts) must be eliminated from this group. True aleukemic myelosis thus becomes a rare disease (Ferrata,[24] Naegeli).

This aleukemic myelosis offers great diagnostic difficulties and may cause diagnostic pitfalls, because there is nothing to indicate the true nature of the disease during life, except microscopic examination of the fluid performed by puncturing the spleen (Hirschfeld, Ferrata).

The chronic form, with the insignificant onset, the slowly progressive anemia, the enlargement of spleen and liver, the pale and grayish brown discoloration of the skin, closely resembles Banti's disease. The more acute form may show hemorrhagic diathesis and great reduction of the blood platelets, suggesting purpura hemorrhagica or essential thrombopenia. In Banti's disease and essential thrombopenia, the removal of the spleen is indicated, and the latest reports on splenectomy in these diseases emphasize the good results. In almost all cases of aleukemic myelosis, however, splenectomy is followed by death, either during the operation or shortly after it. This justifies the detailed report of two cases which I observed within a relatively short period.

REPORT OF CASES

CASE 1.[25]—*History.*—C. W. G., aged 51, a salesman, of German extraction, complained of dizziness, a tired feeling, backache and a dull pain in the splenic region, which had started about six years ago, and had gradually become worse. He also noticed that his color became reddish-brown, and that he lost about 8 pounds (4 Kg.). A blood count, made in the latter part of 1918, gave the following results: hemoglobin content, 89 per cent; erythrocytes, 4,260,000; white cells, 7,600; differential count, normal; no nucleated red cells.

The family history was negative. Four brothers and five sisters were well. His previous illnesses were: blood poisoning at 18 years, scarlet fever at 26 and pneumonia four years before presentation.

Examination.—Physical examination showed him to be fairly well nourished, rather tall, with pale, grayish-brown skin. The abdomen was distended, especially the left upper part. The spleen was greatly enlarged, extending down to about 8 cm. below the umbilicus. It was hard, and along the anterior margin irregular nodular elevations were felt. The liver, also, was distinctly enlarged; its surface appeared smooth. No enlarged lymph glands were palpable. Examination of the lungs gave normal results. The pulse rate was 72, with an irregular beat occasionally. The temperature was normal.

Laboratory Examination.—Two months before admission, examination of the blood revealed: hemoglobin content, 80 per cent; erythrocytes, 3,800,000; 3 normoblasts to 100 white cells; white cells, 7,650; polymorphonuclear leukocytes, 80; lymphocytes, 5; monocytes, 9; eosinophils, 2; basophils, 4; myelocytes, none.

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24. Ferrata, A.: Le Emopatie, parte speciale, Milano, Societa editrice libraria, 1923, vol. 2.

25. From the Grant Hospital, Chicago, Dr. Orth.

On admission, examination of the blood revealed: hemoglobin content, 75 per cent; erythrocytes, 3,640,000; 4 normoblasts to 100 white cells; marked anisocytosis and slight poikilocytosis; a large number of polychromatophils and reticulated erythrocytes. White cells, 7,500; polymorphonuclear leukocytes, 59; lymphocytes, 19; monocytes, 20; eosinophils, 0; basophils, 2; myelocytes, none.

In the urine the specific gravity was 1.010; there was an acid reaction; sugar and albumin were not found. A few leukocytes were found in the sediment.

The blood serum was a normal pale yellow. The direct Van den Bergh test gave a negative reaction; the indirect showed a slight increase of bilirubin (about 1:100,000). There were 110 mg. of cholesterol per hundred cubic centimeters of serum. The antitryptic liter of the serum was normal.

The clinical diagnosis was Banti's disease; and since the large and hard spleen caused considerable discomfort, splenectomy was suggested.

The result of a white blood cell count on the day of the operation was: total number, 7,500; polymorphonuclear leukocytes, 49; lymphocytes, 21; monocytes, 23; eosinophils, 0; basophils, 6; irritation forms, 1; myelocytes, none; 2 normoblasts per hundred white cells. All the polymorphonuclear leukocytes showed mature nuclei, with from three to four segments.

Treatment and Course.—The splenectomy was performed under ether-nitroxyl anesthesia by Dr. Zimmermann and lasted one hour. The patient was weak after the operation and complained of great pain in the abdomen. He died sixteen hours later. Permission for necropsy could not be obtained.

Examination of the Spleen.—Macroscopic observations: The spleen measured 23 by 15 by 7 cm. and weighed 2,667 Gm. The lower pole was bent up toward the hilum. It was of firm consistency. The surface was grayish red and showed irregular, flat and darker elevations. The capsule was thick. At the hilum there was a group of enlarged, reddish gray and firm lymph glands. Their diameter was from 1.5 to 2 cm. On cutting, the spleen was found to consist of a homogeneous, dark grayish red tissue, which projected slightly over the capsule. No follicles or trabeculae were discernible. Irregular, maplike areas, from 2 to 5 cm. in diameter, stood out on account of their deeper red color. Near the hilum there was a spherical node, 2.5 cm. in diameter, which was firmer than the other parts of the spleen. It was dark red, and there were opaque yellow patches and lines in the center.

The enlarged lymph glands were made up of a dark red tissue, in which were found dense whitish areas, from 4 to 7 mm. in diameter.

Microscopic observations: The general structure of the spleen was still preserved. The follicles were small but well demarcated. The sinuses were separated by broad strands of cellular tissue. In some places the tissue was uniformly cellular and sinuses seemed to be absent. When sinuses were found, they were of medium width, lined by a flat or cuboidal endothelium. They contained only a few cells. Sinuses filled with cells were rare. There was no proliferation or desquamation of the sinus endothelium. The tissue between the sinuses consisted of a mixture of various cells. There were many polymorphonuclear leukocytes, eosinophil granulated cells and myelocytes as well as mature forms. Neutrophil myelocytes also were numerous. There were many erythrocytes and groups of nucleated red blood corpuscles with polychromatophil or oxyphilic cytoplasm. Many large cells, resembling in shape, structure and appearance of their nuclei megakaryocytes, were also found. Some of the large cells had one large round or oval nucleus. There was a great variety of smaller round cells with nuclei having a granular arrangement

of the chromatin. Finally, branched cells, with pale nuclei and one or several oxyphilic nucleoli, were present.

The enormous number of granulated cells was most striking in sections stained for demonstrating the oxydase reaction. The follicles only were free from granules.

The cells found in the lumen of the sinuses were leukocytes, myelocytes, lymphoid cells, erythrocytes and erythroblasts. One could observe that the cells entered the sinuses by migrating from the tissue that surrounded them. Often a cell was found wandering through the lining endothelium.

The firm node mentioned above showed the same type of cells. They were embedded with much dense connective tissue. There were old and more recent hemorrhages. The center of the node consisted of fibrous connective tissue, with much granular blood pigment, free and inside of flat cells. Besides the hemosiderin, irregular, wormlike masses of a highly refractive, pale, yellowish-green pigment were observed.

The lymph glands were partly made up of a tissue closely resembling bone marrow. This tissue seemed to infiltrate the glands from the hilum, and the medullary portion showed no lymphatic structures. The cortex was better preserved, and cortical follicles still were visible. In the medulla were found all the cell types described in the splenic pulp. Giant cells were numerous, also eosinophil and neutrophil myelocytes and leukocytes. Nucleated red blood corpuscles were less numerous than in the spleen. Between the cells there was a loose fibrillar network, which in many places became abundant. In the areas appearing whitish to the naked eye, the fibrillar connective tissue predominated. But here, also, the large number of giant cells was striking.

The marginal sinuses were distended and contained many swollen and desquamated endothelial cells, which often had engulfed débris of red and white blood corpuscles and blood pigment. The lymphatics at the hilum were filled with lymphoid cells and bone marrow cells, especially myelocytes.

Cultures from the splenic pulp were made on blood-agar plates, in plain broth and dextrose broth, both aerobically and anaerobically. All cultures remained sterile.

Summary.—Myeloid metaplasia of the splenic pulp, with circumscribed fibrosis, hemorrhages and hemosiderosis; myeloid metaplasia of the lymph glands at the hilus of the spleen with fibrosis; aleukemic myelosis.

CASE 2.[26]—*History.*—A white man, aged 43, developed bleeding from the nose four weeks previous to entrance at the hospital. This hemorrhage lasted for four hours, recurred the next day and required packing. The patient had since been weak and confined to his bed. The bleeding recurred at irregular intervals. Subcutaneous hemorrhages on the arms and legs were noted later. His ailment progressed rapidly. He vomited blood, and his gums started to bleed.

Examination.—A blood count made on the day of his admission to the hospital gave the following result: red blood corpuscles, 900,000; hemoglobin content, 22 per cent; color index, 1.2; white cells, 4,350; polymorphonuclear leukocytes, 59; lymphocytes, 35; monocytes, 5; eosinophil leukocytes, 1; myelocytes, none. There were marked anisocytosis and poikilocytes, many polychromatophils and no normoblasts. The blood platelets numbered 30,000. The bleeding time (Duke's method) was plus sixty-nine minutes.

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26. From the service of Dr. Williamson of the Research and Educational Hospital, University of Illinois. The clinical and hematological observations of this case will be reported in detail by Dr. C. L. Birch.

Treatment and Course.—After two blood transfusions of 540 and 600 cc. of blood, respectively, the blood count was: hemoglobin content, 27 per cent; erythrocytes, 1,650,000; white cells, 5,600; platelets, 80,000.

The transfusion was repeated, and 500 cc. of blood was given. One and one-half hours later, the patient had a severe chill, lasting for thirty minutes, associated with severe pains in the left side of the chest. The temperature rose to 102.4 F. The next day the blood count was: hemoglobin content, 42 per cent; erythrocytes, 2,440,000; white cells, 4,850; platelets, 75,000. The bleeding time was nine minutes. A third transfusion of 600 cc. of blood again was followed by a chill and a rise of temperature to 104 F.

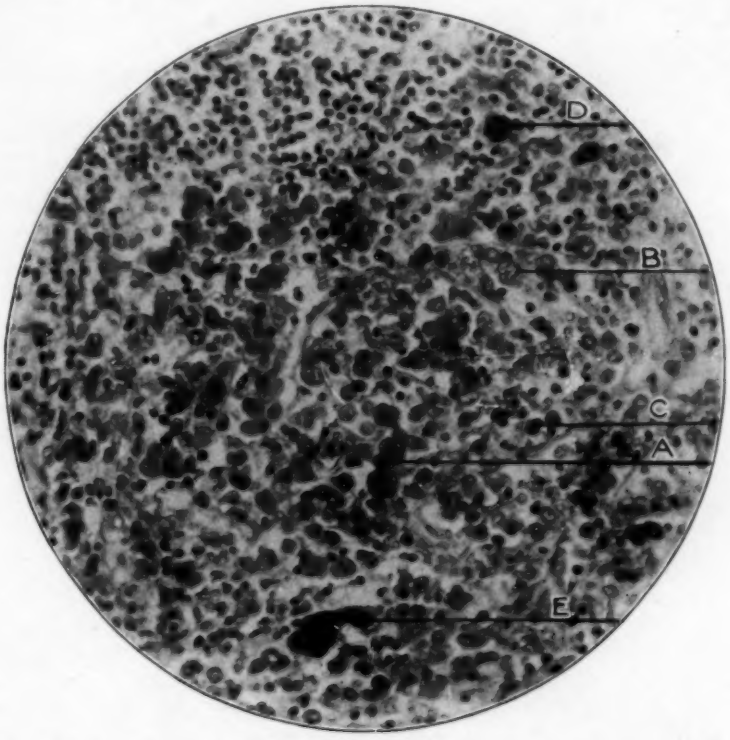

Fig. 1.—Spleen from case 2; *A* indicates syncytium-like cell masses; *B*, hypertrophic reticulum cells (hemohistoblast); *C*, erythroblast; *D*, hyperchromatic giant mitosis; *E*, giant cell with hyperchromatic structureless nuclei. Fixation with Zenker-Maximow solution, paraffin section, hemalaun-eosin stain; × 275.

Blood cultures were made and remained sterile.

The urine did not contain albumin, blood and sugar.

A markedly enlarged spleen and a systolic murmur at the apex of the heart were found.

The clinical diagnosis was thrombopenic purpura.

Thirteen days after admission to the hospital, a laparotomy was made. The patient died during the attempt to remove the huge spleen.

Necropsy.—This was performed four hours after death.

The body was that of a white man, 66 inches (167 cm.) long, weighing 124 pounds (56 Kg.). The skin was pale, almost white, and there was just a trace of livid patches on the back. In the skin of both arms, of the right upper part of the abdomen, and of the right thigh, multiple deep red hemorrhages, from 1 to 3 cm. in diameter, were found. The skin of the right fossa cubitalis was diffusely violet. The nostrils and the lips were covered with coffee-brown, thick, foamy fluid. From the anus tarlike masses escaped. There was a fresh operation wound in the left hypogastric region.

The muscles of the chest were deep reddish-brown and rather dry. There was a fair amount of subcutaneous fat tissue.

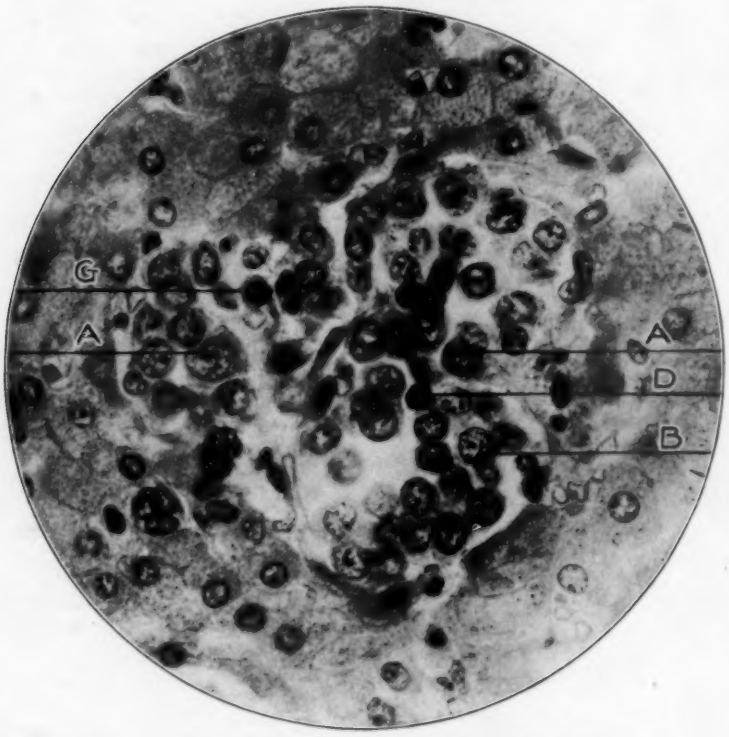

Fig. 2.—Liver from case 2; intracapillary cell nest; *A* indicates hypertrophic proliferating Kupffer cells; *B*, myeloblasts; *C*, mitosis; *D*, erythroblast. Technic same as in figure 1; × 560.

The weight of the thyroid was 51 Gm. The tissue was pale and contained much colloid. The parathyroid glands stood out distinctly because of their deep brown color. The mucous membrane of the pharynx was pale and covered with a dark brown fluid. The tonsils were small and showed no ulceration.

There was a small amount of clear yellow fluid in both pleural cavities. The lungs were adherent about the apexes, which contained small scars. The lung tissue was dry and anemic.

The heart was covered by bright yellow fat tissue. Multiple red hemorrhages were found in the epicardium of both ventricles. The heart weighed

360 Gm. The wall of the left ventricle was 20 mm., and that of the right ventricle 8 mm., thick. The myocardium was grayish brown and friable. The ventricles were distended and filled with dark red liquid blood, that coagulated after removal. The heart valves were normal.

The circumference of the aorta was 66 mm. above the valve, 45 mm. at the diaphragm and 36 mm. at the bifurcation. There were small hyaline plaques in the abdominal part and larger fatty plaques in both coronary arteries.

The intestinal loops were distended. Deep brown masses shone through the wall. The abdominal cavity contained about 800 cc. of a red, bloody fluid and soft red blood clots about the spleen.

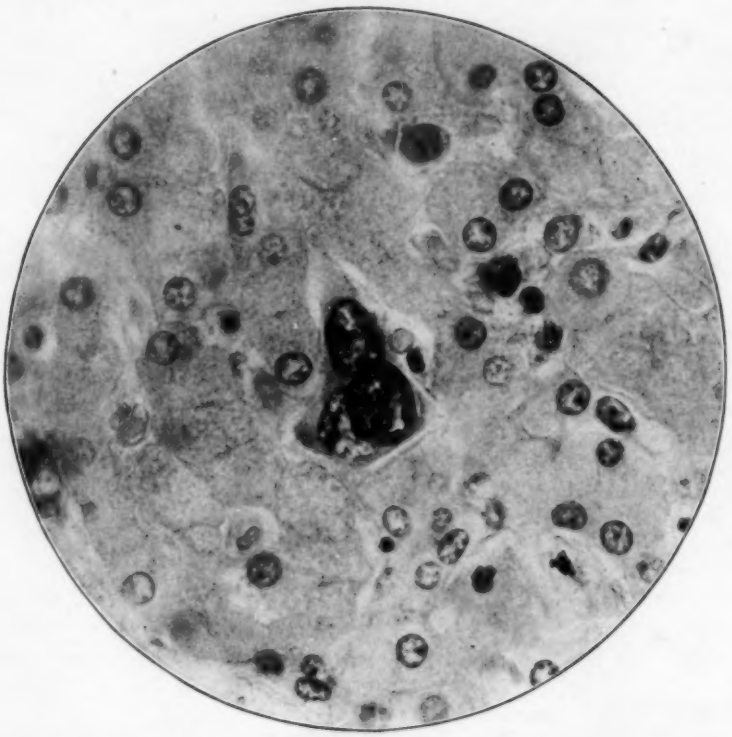

Fig. 3.—Giant cell in portal capillary, case 2. Technic same as in figure 1; × 650.

The liver was misplaced to the deeper parts of the right hypochondrium. The weight amounted to 2,090 Gm. It was quite firm. The surface was smooth and grayish brown, with linear whitish scars in the capsule. The structure was indistinct. The gallbladder was filled with thin, yellowish brown bile.

The spleen weighed 1,175 Gm. and measured 20 by 6 by 12 cm. Its capsule was grayish red and its surface was studded with numerous dark red nodules, from 3 to 4 mm. in diameter. The nodules had a granular surface. The spleen was of rather firm consistency. Cross-sections through the spleen showed a uniform deep red pulp, with small, grayish white follicles. Trabeculae were not discernible.

A large number of spherical nodes, resembling the spleen in gross appearance, were found around the tail of the pancreas, along its upper margin and embedded

in the large omentum. The nodes had a diameter of from 1 to 2.5 cm. and a smooth, reddish brown surface.

At the hilum of the spleen, there was a group of enlarged deep red, soft lymph glands. Similar glands were found about the hilum of the liver and about the aorta. Here they formed a solid, deep red plate, from 1 to 3 cm. thick.

The weight of the right suprarenal was 5, that of the left 7 Gm. The cortex was bright yellow.

The right kidney weighed 200, the left 160 Gm. The surface of the kidneys was smooth and pale. There was a small hemorrhage in the pelvis of the right kidney.

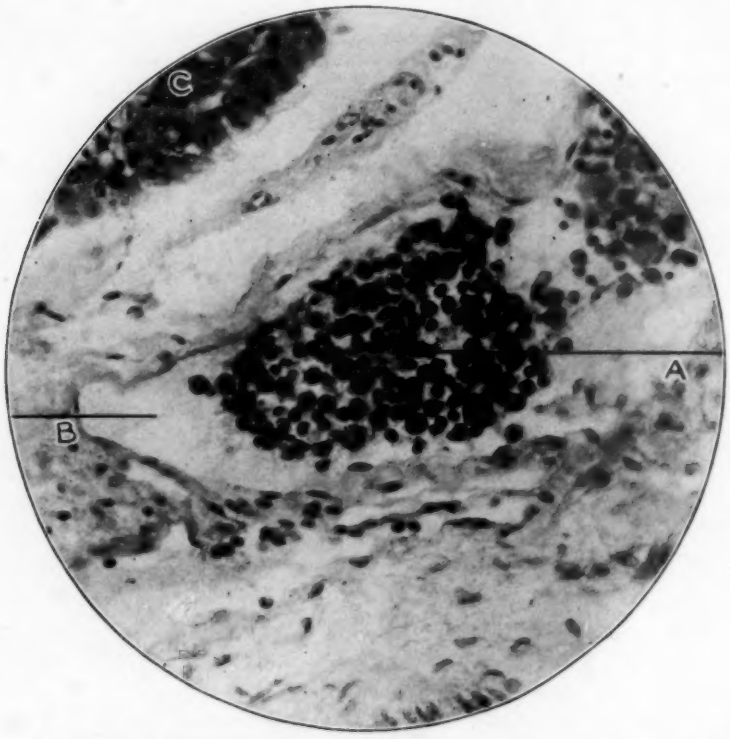

Fig. 4.—Pancreatic lymph vessels from case 2; *A* indicates a group of myeloid cells; *B*, lymph vessel; *C*, pancreas tissue. Fixation with 10 per cent liquor formaldehydi. Paraffin section, hemalaun-eosin stain; × 275.

The right testicle weighed 20, the left 15 Gm.

The stomach contained much coffee-brown fluid. The mucosa of the fundus showed many fresh, deep red hemorrhages.

The intestine was filled with tarlike masses. Its mucosa was pale.

The bone marrow in the middle of the femur was soft and deep red, with small areas of yellow fat tissue.

Permission to open the skull was not obtained.

Cultures made from the spleen and the bone marrow remained sterile. From the heart blood, a gram-negative bacillus belonging to the proteus group was cultivated. It was, no doubt, a contamination.

Histologic Examination.—The normal microscopic picture of the spleen was greatly changed. The malpighian bodies were reduced to small accumulations of lymphocytes, which were embedded with a cellular tissue. Sinuses could not be distinguished. A large number of red blood corpuscles and of nucleated cells of various shapes and structures were present. The cells tended to form accumulations, in which one type of cell was predominant. In the periphery of these areas, the different types of cells mingled with each other.

The large number of nucleated red blood corpuscles was striking. Many of them were larger than normal erythrocytes, had a bright brick-red or polychromatophil cytoplasm and one or more deeply stained nuclei. The nuclei often showed buds of chromatin projecting from their periphery into the cytoplasm.

Besides the nucleated red blood corpuscles and erythrocytes of various sizes, there were groups of cells with a scanty basophilic cytoplasm and large round nuclei, having a distinct granular chromatin structure. The nuclei contained one or several small basophilic nucleoli. These cells often were so densely packed together that they appeared as syncytia. There were many mitotic figures, with short, clumsy and irregular chromosomes.

These cells seemed to be derived from large round, oval or branched elements, the cytoplasm of which was delicate and stained pale blue with Romanowsky's stains. They had large round nuclei, with loose chromatin granules that accumulated near the membrane. The nuclei contained from one to three large oxychromatic nuclei. At times these cells also developed to huge forms, with one or several large, irregular nuclei. The nuclei often stained so deeply that no structure could be made out. When there were several nuclei, they bordered on, but did not seem to be connected with, each other. Giant mitoses were also found, with the most irregular arrangement of the heavily stained chromosomes.

Finally, there were numerous eosinophil myelocytes and few neutrophil myelocytes and plasma cells.

The results of the oxydase reaction (Graham's alpha naphthol-pyronin stain) were as follows: Only a few cells contained a granulation giving this reaction. They appeared as single round elements with many fine purple granules, which sometimes were piled up in one place. Some cells had granules of different sizes, the large ones being irregular in shape and staining less distinctly. Oxydase granulation was also observed occasionally in a giant cell. The granules appeared in irregular patches. When the cells formed syncytia, they had no granulation.

The histologic picture of the aberrant spleen was identical with that of the main organ.

The lymph glands about the hilum of the spleen and of the liver, and along the abdominal aorta, greatly resembled the spleen. Most of the lymphatic tissue was replaced by immature and atypical blood cells. There were many giant cells. Erythropoiesis was less extensive than in the spleen. The marginal sinuses were filled with cells and with blood pigment, free and engulfed by cells with pale nuclei.

The portal capillaries of the liver were filled with the different types of cells described in the spleen. These cells either lay singly or formed nodules, expanding the capillaries and causing atrophy and destruction of the adjacent liver cells. The intracapillary cellular nodules appeared to be derived from enlarged Kupffer cells. Accumulations of cells were also observed in the smaller portal septums. Giant cells were numerous; so also were nucleated red blood cells, which, however, did not form larger nodules.

Fatty and cellular areas alternated with each other in the bone marrow, but the latter prevailed. There was much active erythropoiesis, with many mitotic

figures showing the characteristic pointed angles. Some of the erythroblasts were large and irregular. There were syncytia of cells with scanty cytoplasm, and large cells with pale nuclei and oxyphilic nucleoli. Many giant cells were present. Some of these were large and atypical.

The lipoid content of the suprarenal cortex was much reduced. In the reticularis there were areas of increased interstitial connective tissue resembling scars. In some places the capillaries of the internal fasciculate contained groups of large round cells with scanty homogeneous basophilic cytoplasm and deeply stained nuclei.

In the kidney single large basophilic cells with dark nuclei were found in the glomerular tufts and in the capillaries about the convoluted tubuli.

There was an increased amount of loose connective tissue about the large blood vessels of the heart. It contained a few large basophilic cells. The muscle fibers in some places contained fine fat granules.

In the alveolar capillaries of the lungs, a large basophilic cell with deeply stained nucleus or nuclei without cytoplasm was occasionally found.

The lymph vessels in the peripancreatic and interstitial fat tissues were distended and crowded with immature blood cells and giant cells.

The vesicles of the thyroid were wide and filled with homogeneous oxyphilic colloid. The epithelial lining was flat.

There was no spermogenesis in the testicles. The tubules were lined by indifferent epithelium. In the center, there were collapsed tubules, with thickened basal membrane and without epithelium. In some of the tubules of the epidydimis a few degenerated spermatozoa were found.

The prostate showed circumscribed areas of epithelial metaplasia, with proliferation of the basal cells.

Nowhere in the larger blood vessels of the different organs was there any accumulation of immature blood cells. Here and there a few abnormal cells were noted. These cells stained poorly, their nuclei had lost their structure, and there were degenerated nuclei without protoplasm.

Anatomic Diagnosis.—Acute aleukemic myelosis; extensive myeloid metaplasia of the spleen, liver and abdominal lymph glands; aberrant spleens about the pancreas and in the large omentum; foci of blood formation in the cortex of the suprarenal; recent hemorrhages in the skin, epicardium, gastric mucosa, and pelvis of right kidney; beginning fatty degeneration of the myocardium; ascites, bilateral hydrothorax.

COMMENT

The excessive proliferation of the myeloid tissue described in the two cases had caused no characteristic changes of the blood picture, and the true nature of the disease was revealed only by the histologic study of the organs involved. In both cases, therefore, the diagnosis of "aleukemic myelosis" was made. Ferrata calls the condition a "closed myelotis," because the proliferating immature cells of the bone marrow do not find their way into the blood streams. Indeed, the absence from the blood of the cells growing so luxuriously in the places of blood formation is the most striking feature of the disease. It is of much greater significance than the low count of white blood cells in general.

1. *The Etiology of Aleukemic Myelosis.*—The etiology is just as unknown as is the cause of the leukemic type. There appears in the

literature of recent years an increasing amount of evidence in favor of an infectious origin of certain forms of leukemia, in particular of the acute myeloblast leukemia, in which positive bacteriologic observations frequently have been obtained (Sternberg,[27] Catsara,[28] and others). On the other hand, blood changes suggesting leukemia are sometimes obtained in severe septic conditions.

The result of the bacteriologic examination in the two observations reported was negative. In the first case, cultures were made from the spleen immediately after the operation. In the second case, blood during life and after death, splenic tissue and bone marrow were used for cultures. Only the cultures taken from the heart blood after death showed some growth which proved to be a contamination. The negative results in the acute case are of special interest, since gangrenous or ulcerative processes in the oral cavity and throat were absent, thus excluding the possibility of secondary invaders.

2. *The Microscopic Anatomy of Aleukemic Myelosis.*—The histologic changes were similar to those observed in leukocythemic leukemia. The erythropoiesis was extensive, and in the acute case had led to the formation of megaloblasts. The large number of nucleated red cells had also caused a macroscopic appearance of the bone marrow somewhat different from what is described as typical of myelogenous leukemia. It was not yellowish gray (Neumann) nor yellowish red (Naegeli), but deep purple red. Extensive erythropoiesis is also found occasionally in leukemic myelosis (Svend,[29] Hirschfeld).

Fixation of fresh tissue in warm neutral formalin and Zenker's solution secured excellent fixation in both cases and made possible a careful study of the histogenesis of the myeloid cells. It is not the purpose of this paper to enter into a detailed description of the development of the blood cells in leukemia. The literature on this subject is enormous and has recently been reviewed repeatedly, especially in the larger monographs on blood diseases (Ferrata, Hirschfeld, Naegeli, Pappenheim). Only a few observations will be discussed.

In the spleen of the chronic aleukemic myelosis the blood cells were formed in the tissue between the sinuses from reticular cells. They entered the lumen by passing through the wall. There was no transformation of the sinus endothelium to myeloblast, erythroblast or giant cells. This indicates a difference between the endothelium of the sinuses and

27. Sternberg, C.: Ueber akute Leukaemie, Wien. klin. Wchnschr. **33**:553, 1920.

28. Catsara, J.: Beitrag zur Frage ueber die infektioes-toxische Natur der leukaemischen Erkrankungen, Virchows Arch. f. path. Anat. **249**:43, 1924.

29. Svend, Petri: Etude histologique d'un cas de leucemie myeloide, avec differentiation des diverses varietes de cellules par mesurage des angles de sommet des mitoses, Acta path. et microbiol. Scandinav. **1**:37, 1924.

the reticular cells of the pulp, which is evident also from other observations on the microscopic anatomy of the spleen and the genesis of the blood cells.

The spleen and the lymph glands showed marked fibrosis in some places. Giant cells became surrounded and isolated by dense connective tissue; and when a large number of eosinophil myelocytes and leukocytes accumulated about them, the histologic picture was similar to that of Hodgkin's disease. That the tissue changes in myelogenous leukemia sometimes may resemble the lymphogranuloma has been brought out recently by Symmers.[30]

In the acute case, the spleen had almost entirely lost its structure. Many of the cells were irregular and different from any kind of cell observed in normal blood-forming tissue even during embryonic life. The large number of abnormal giant mitoses was suggestive of a malignant new growth. The proliferating cells had broken through the capsule of the spleen, producing granular outgrowths on the surface. These changes were not due to rupture of the capsule, because the capsule was rather thick. It is thought that the protruding splenic tissue had given rise to the numerous aberrant spleens in the abdominal cavity, by way of implantation of small bits of pulp.

Examination of many slides stained by various methods suggests the following histogenesis of the myeloid cells of the spleen in this case: The stem cell is a rather large round, oval or branched cell, with a delicate homogeneous cytoplasm and a loose nucleus with large, distinct nucleoli. This cell is regarded as a hemohistoblast (Ferrata, Eposito,[31] Richter [32]), derived from hypertrophic reticular cells. As shown by the transitional stages, it produces smaller cells, with denser and more basophilic cytoplasm and more compact nuclei. These cells often seem to be connected with each other and form syncytia-like masses. Most of the cells are not granulated. Here and there a single cell may be observed with more distinct outlines and a fine or coarse and irregular granulation, giving a positive oxydase reaction. More numerous, and in certain places predominating, are cells with a distinct, coarse oxyphilic formation. In some places the cells take up a violet or bright brick coloration and their nuclei become dark (erythroblasts and megaloblasts). Single cells grow to become huge elements with irregular nuclei. Thus, all cells ultimately take their origin from indifferent reticular cells. This explanation, as far as the white blood cells are concerned, is in

30. Symmers, D.: The Clinical Significance of the Pathological Changes in Hodgkin's Disease, Am. J. M. Sc. **167**:313, 1924.

31. Eposito, A.: Morfologia e significato anatomico degli emoistioblasti nelle leucemia, Hematologica **4**:269, 1923.

32. Richter, M. N.: Observations on the Hemohistioblasts of Ferrata, Am. J. M. Sc. **169**:336, 1925.

accordance with the classic studies of Sabin, Cunningham and Doan [33] on the development of the blood cells. I was not convinced, however, that the erythroblasts have a different origin, namely, from the endothelial cells, as has been described in the bone marrow of pigeons and rabbits during regeneration (Cunningham and Doan [34]). In leukemia, at least, there exists one uniform original cell for all the different forms of bone marrow cells.

In the liver, the Kupffer cells gave rise to the intracapillary accumulation of blood cells. I believe that the Kupffer cells of the liver with their branches crossing the lumen of the portal capillaries (Zimmermann) are more closely related to the reticulum cells than to the endothelial cells of the blood-forming organs.[35]

While the numerous giant cells in the spleen and lymph glands of the chronic case resembled bone marrow giant cells, they were atypical in the acute myelosis. Here they sometimes contained oxydase granules, suggesting that they might be abnormal hypertrophic myeloblasts. Similar giant cells also were described occasionally in leukemic myelosis (Barth,[36] Koerner [37]).

3. *Negative Observations in the Blood.*—Different attempts have been made to explain the aleukemic blood picture in certain cases of leukemia. It is thought that the lack of a chemotactic stimulant prevents the entrance of the newly formed cells into the blood stream (Pappenheim and his school, Baar,[38] F. Kohn and others). Others believe that in the aleukemic cases the new growth of the blood-forming tissues is

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33. Cunningham, R. C.; Sabin, F. R., and Doan, C. A.: The Development of Leucocytes, Lymphocytes and Monocytes from a Specific Stem Cell in Adult Tissue, Contributions to Embryology, no. 84. Doan, C. A.; and Cunningham, R. C., and Sabin, F. R.: Experimental Studies on the Origin and Maturation of Avian and Mammalian Red Blood Cells, ibid.

34. Doan, C.: On the Intravascular Development of Erythrocytes in the Bone Marrow of the Adult Pigeon, Proc. Soc. Exper. Biol. & Med. **20**:269, 1923. Cunningham, R. C., and Doan, C. A.: On the Intravascular Development of Erythrocytes in the Bone Marrow of Adult Rabbit, ibid. **20**:262, 1923.

35. No conclusions should be drawn from the histologic observations in leukemia on the extramedullary blood formation in general. In leukemia there is a profound change of the proliferative and prosoplastic potencies of the entire indifferentiated mesenchymatous tissue. This change has more in common with neoplastic processes than with plain regeneration or hypertrophy of the blood-forming tissue that occurs in anemia following abnormal blood destruction or loss of blood, or in infection and inflammation.

36. Barth: Ueber Riesenzellenbildung bei Leukaemie, Virchows Arch. f. path. Anat. **256**:693, 1925.

37. Koerner: Auffalende Rieszenzellenbefunde bei akuter Myeloblastenleukaemie, Virchows Arch. f. path. Anat. **259**:617, 1926.

38. Baar, H.: Ueber akute aleukozytaemische Leukaemie im Kindesalter, Jahrb. f. Kinderh. **104**:1, 1924.

so atypical as to cause a loss of the proper connection with the blood channels, making it impossible for the cells to get into the circulating blood. In the second of the cases described in this paper, the myeloid cells often formed syncytia, which observation may account in part for their not being able to enter the blood. Besides, severe degenerative changes were found in the few abnormal blood cells inside the large blood vessels. In the lymph vessels of the upper abdominal cavity, well preserved immature blood cells were observed. This points to a destruction of the cells should they appear in the blood. Szilard described a diminished resistance of the myeloid cells in leukopenic leukemia.

Several different mechanisms in persons with leukemia, as in normal persons, probably determine the composition of the blood. The acitvity of these mechanisms may change during the course of the disease, and thus the blood picture may vary. King reports that of the sixty-four cases of chronic myelogenous leukemia in the records of the Johns Hopkins Hospital, three were spontaneously aleukocythemic at some stage. Repeated blood examination in such cases will finally secure a correct diagnosis. In true aleukemic myelosis, however, the white blood picture remains normal.

In aleukemic myelosis a more or less severe anemia is always present, and in several reports the large number of normoblasts or the occurrence of megaloblasts has been emphasized (Hirschfeld). Since the color index may amount to more than 1, the blood observations resemble those of pernicious anemia. I think that the cases described as pernicious anemia with transformation to myelogenous leukemia were aleukemic forms of leukemia, which finally developed leukemic blood changes. In children, nucleated red cells often are missed, and the leukemia may be mistaken for an aplastic anemia (Baar, Abt [39]).

4. *The Clinical Diagnosis of Aleukemic Myelosis.*—Because the blood examination fails to give any information as to the underlying pathologic condition, puncture of the spleen has been recommended by Hirschfeld, Ferrata and others. The hematologic examination of the splenic fluid, no doubt, will reveal the cellular composition of this organ. In chronic cases, in which the spleen is firm and its capsule thick, there is no danger in puncturing the spleen with a fine needle; but in the more acute cases, in which the rapidly increasing pulp may spontaneously break through the capsule, and in which there is a great tendency to bleed, the puncture is contraindicated. So far as I know, no effort has yet been made in aleukemic leukemia to lure the abnormal splenic cells into the peripheral blood by means of a mild stimulation of this organ through weak irradiation or the injection of epinephrine.

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39. Abt, J.: A Case of Aleukemic Leukemia with Clinical Symptoms of Aplastic Anemia, M. Clin. N. Amer. **8**:427, 1925.

During the operation, the peculiar appearance of the enlarged deep red lymph glands at the hilum of the spleen and of the spleen itself may attract the attention of the surgeon. Under such conditions, it might be indicated not to remove the spleen.

5. *Prognosis.*—Aleukemic myelosis is a fatal disease, as is the leukemic form. Chronic cases may be unrecognized for several years. The acute type leads to death within a few months from the onset. Gutmann,[40] not long ago, reported a case of what he called "leukopenic leukaemia" with recovery. However, the possibility of an obscure septic condition cannot be excluded from his description, and the same holds true of other similar observations (Decastello [41]).

6. *Therapy.*—Until a few years ago, splenectomy was regarded as strictly contraindicated in the various forms of leukemia (Krumbhaar,[42] 1918). This standpoint still is represented by the French school of hematologists. Jolly [43] wrote in 1925: "Le chirurgien qui enlève une rate leucémique ou qui enlève une rate sauve apres s'etre assuré a l'avance par un examen histologique du sang, que son malade n'est pas leucémique, commet une faute grave qui engage sa responsibilité." (The surgeon who removes a leukemic spleen, or who removes a spleen without assuring himself in advance by a histologic examination of the blood that the patient is not leukemic, commits a serious error, for which he may be held accountable.) German and especially American writers are less pessimistic (Seefisch, Herfarth, Vogel, Toenniessen,[44] Campos [45] and Giffen [46]). W. J. Mayo [47] saw only one death in twenty-nine cases of splenomyelogenous leukemia in which the spleen had been removed, and great temporary benefit in the other cases. Giffen brought out the value of a preceding irradiation of the spleen.

In aleukemic myelosis, however, splenectomy always seems to be fatal, and the patients die during the operation or soon after (Berblinger,

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40. Gutmann, B.: Leukemia; Report of an Atypical Case, Am. J. M. Sc. **167**:718, 1924.

41. Decastello: Akute Leukaemie und Sepsis, Wien. Arch. f. inn. Med. **11**: 217, 1925.

42. Krumbhaar, E. B., in Pearce, Krumbhaar and Frazin: The Spleen and Anemia, Philadelphia, J. B. Lippincott Company, 1918.

43. Jolly, J.: Leucemie myeloide et splenectomie, Compt. rend. Soc. de biol. **92**:471, 1925.

44. Toenniessen, E.: Ueber den Verlauf der Leukaemie nach Milzextirpation, München. med. Wchnschr. **67**:1059, 1920.

45. Campos, E. D.: Sur un cas de myeloleucemie chronique avec splenectomie, Compt. rend. Soc. de biol. **92**:307, 1925; Leucemie Myeloide et Splenectomie, ibid. **93**:143, 1925.

46. Giffen, H. Z.: Splenectomy Following Radium Treatment for Myelocytic Leukaemia, M. Rec. **94**:1020, 1918.

47. Mayo, W. J.: Splenic Syndrome, Brit. M. J. **2**:122, 1923.

Goia, Hirschfeld, Keuper and others). The patient mentioned by Krumbhaar lived for two weeks after the operation, but the condition was not an aleukemic leukemia (although the white cells numbered only from 10,000 to 15,000) because myeloid cells were found.

In the two cases reported, the splenectomy was fatal. The operation was undertaken in the assumption of a Banti's disease or essential thrombopenia being the underlying pathologic condition. The great importance of considering an aleukemic myelosis in the differential diagnosis of obscure enlargements of the spleen has already been emphasized.

Irradiation of the spleen, also, seems to be of no value (Szilard, Schwarz).

Blood transfusion in the more acute cases has sometimes been recommended. I have observed only that it hastened the downward course of the disease.

SUMMARY

Aleukemic myelosis not only is characterized by a normal or subnormal total number of the white cells of the blood, but also by a normal differential count. Immature forms of granulocytes either are entirely absent or appear in a low percentage at irregular intervals. Thus, the blood picture gives no information as to the extensive proliferation of the myeloid tissue.

A low white count is not sufficient to make the diagnosis aleukemic myelosis. Acute myeloblast leukemias frequently show only a slight rise in the number of white cells or no increase at all. A differential count will secure the correct diagnosis at once.

As in leukemic myelosis, an acute and a chronic form exist. Both offer great diagnostic difficulties. The chronic form may be mistaken for Banti's disease and the acute form for a thrombopenic purpura. These mistakes prove fatal if splenectomy is performed.

The histologic examination of the spleen in these cases reveals extensive myeloid metaplasia of the pulp.

SPONTANEOUS BONE AND MARROW FORMATION IN THE AORTA OF A RABBIT*

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Miles [1] first called attention to the occurrence of spontaneous arteriosclerosis in rabbits. The condition has been studied carefully since. Nevertheless, spontaneous bone and marrow formation has not been reported in the aorta of the rabbit, although it is not an uncommon

Spontaneous bone in aorta of rabbit.

observation in arteriosclerosis in human beings. Experimentally, Harvey [2] has induced bone and marrow formation in the abdominal aorta of rabbits by painting the outside of the vessel with a 3 per cent solution of silver nitrate and a 2 per cent solution of copper sulphate.

In a series of thirty rabbits in which the ascending limb, arch and first part of the descending limb of the aorta were examined microscopically, spontaneous lesions were observed in eight of the animals, or 27 per cent. In one of these, spontaneous bone and marrow formation was also encountered.

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* From the Department of Pathology, Medical School of Harvard University.

1. Miles, Amy B.: Spontaneous Arterial Degeneration in Rabbits, J. A. M. A. **49**:1173 (Oct. 5) 1907.

2. Harvey, W. H.: Experimental Bone Formation in Arteries, J. M. Research **12**:25, 1908-1909.

This animal was an adult male of unknown age, weighing 2.5 Kg., which had been purchased from the animal farm. It was an unusually agressive animal and attacked any one who opened its cage.

The lesion was not observed in gross, as the chest organs were removed in toto and fixed in Zenker's fluid. On microscopic examination of the arch of the aorta for a distance of 7 mm., practically complete destruction of the normal structure of the media was discovered. Foci of hyalinization, calcification cartilage and bone and marrow replaced the elastic tissue and muscle cells. The thickness of the wall varied from one-half to one and one-half times that of the adjacent normal aortic wall. The accompanying photomicrograph shows the most perfect portion of bone formation with the central marrow containing all types of young blood cells.

Laboratory and Technical Notes

THE QUANTITATIVE DETERMINATION OF ETHYL ALCOHOL IN HUMAN TISSUES*

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The problem of finding a good method for the quantitative determination of small amounts of alcohol has interested many workers for some time in the past. Several methods have been developed and recommended, and, according to the principles on which they are based, may be classified in six groups. We have made a critical survey of all these methods, have studied them experimentally, and have come to the following conclusions:

Group 1.—These methods are based on the oxidation of the alcohol to acetic acid and titration of the latter. V. Subbotin,[1] in 1871, was the first one to use this principle. He heated the alcohol solution with sulphuric dichromate mixture on a sand bath for twenty-four hours, then distilled the acetic acid and titrated it. The defects in the method are: (*a*) In the prolonged heating some of the acetic acid produced is oxidized to carbon dioxide and hence lost. (*b*) The optimum amounts of sulphuric acid and dichromate to be used were not determined. The latter is essential, as will be shown later. (*c*) A twenty-four hour heating is too time-consuming for routine work.

Group 2.—There are methods depending on the titration of the alcohol by a standard solution of dichromate sulphuric acid.

Bodländer[2] titrated a definite amount of a standard solution of dichromate-sulphuric acid (while hot) with the solution of alcohol until a green color was obtained.

Strassman[3] made use of colorimetric comparisons, with solutions of alcohol of definite strengths, using Bodländer's principle of the change of the dichromate from orange to green.

Benedict and Norris[4] completely oxidized all the alcohol by an excess but measured amount of a standard solution of dichromate-sulphuric acid. They then reduced the chromic acid that was left by an excess but known amount of a standard solution of ferrous ammonium sulphate. Next they titrated the solution of ferrous ammonium sulphate that was in excess by a standard solution of potassium permanganate until a pink end-point was obtained.

Nicloux[5] compared the color, which he obtained on adding the alcohol solution to a definite solution of chromic-sulphuric acid, with the colors produced by a series of known strength solutions of alcohol treated in the same way.

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* From the Chemical Laboratories of Bellevue Hospital Medical College and Washington Square College, New York University, and of the Chief Medical Examiner's Office of the city of New York.

1. Subbotin, U.: Ztschr. f. biol. Chem. **7**:361, 1871.
2. Bodländer: Pflüger's Arch. f. d. ges. Physiol. **32**:398, 1883.
3. Strassman: Pflüger's Arch. f. d. ges. Physiol. **49**:315, 1891.
4. Benedict and Norris: J. Am. Chem. Soc. **20**:293, 1898.
5. Nicloux: Compt. rend. Soc. de biol. **3**:841, 1906.

Cotte[6] determined the alcohol by adding an excess but known amount of standard chromic sulphuric acid, and then titrated the excess by standard ferrous ammonium sulphate, using potassium ferricyanide as an outside indicator.

Baudrexel[7] distilled the alcohol into a measured amount of standard chromic sulphuric acid and then titrated the excess of chromic acid with a standard solution of alcohol.

Nicloux[8] titrated the alcohol solution directly with a standard solution of chromic sulphuric acid until the green first obtained changed to a brown-green.

Barendrecht[9] oxidized the alcohol with an excess of a standard solution of alkaline permanganate; then he reduced the excess permanganate by adding an excess of standard oxalic acid, and finally he titrated the excess of oxalic acid by a standard solution of permanganate.

Widmark[10] used a method much the same as that of Baudrexel, outlined above.

Kumao Yamakami[11] recommends the Nicloux method, which he has modified slightly.

All the methods in this group depend on the use of standardized oxidizing agents and reducing agents. Among the defects may be listed:

(*a*) The standard solutions, being oxidizing or reducing agents, change rapidly. They must be restandardized daily. The chromic sulphuric acid standard rapidly absorbs vapors of moisture and alcohol from the atmosphere.

(*b*) The oxidation of the alcohol does not always follow one well defined equation. Under various conditions there may be formed acetaldehyde, acetic acid and carbon dioxide in various proportions. If a method like the foregoing is used, all conditions, as well as the proportion of reagents, must always be the same.

(*c*) Some acetaldehyde is always lost by vaporization during the titration.

(*d*) In most of the foregoing group, the end-point is difficult to perceive, is not sharp and has little precision. Errors of from 10 to 20 drops often occur.

(*e*) In the case in which a better end-point has been obtained (Benedict and Norris) it has been done only by greatly increasing the number of steps in the determination. The method then becomes too cumbersome.

(*f*) In tissue distillates, volatile organic matter (other than alcohol) is present, which also tends to reduce the standard dichromate solution.

Group 3.—These methods depend on the oxidation of the alcohol to acetaldehyde and then ascertaining the amount of the latter colorimetrically by reduced fuchsin.

Argenson[12] oxidized the alcohol to acetaldehyde and then added reduced fuchsin, comparing the red color obtained with a series of standardized permanganate solutions.

The two main objections to a method based on this principle are: (*a*) In the mild oxidation of alcohol, not only is acetaldehyde obtained, but invariably a large amount of acetic acid is produced.

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6. Cotte: Répert. de pharm. **9**:438, 1852.
7. Baudrexel: Wchnschr. Brauerei **28**:21, 1912.
8. Nicloux, cited by Schweisheimer: Deutsches Arch. f. klin. Med. **109**: 272, 1913.
9. Barendrecht: Ztschr. f. anal. Chem. **52**:167, 1913.
10. Widmark: Skandin. Arch. f. Physiol. **35**:125, 1917.
11. Yamakami: Tohoku J. Exper. Med. **4**:275 (July 23) 1923.
12. Argenson: Bull. Soc. chim. **27**:1000, 1902.

(*b*) The colorimetric test with reduced fuchsin can be applied only to small traces of acetaldehyde. For this reason, only a small fraction of the entire distillate is used for the color comparison. On calculating for the amount present in the whole distillate, any error in the colorimetric estimation becomes magnified many times.

Group 4.—The methods in this group depend on the formation and estimation of iodine derivatives of the ethyl alcohol.

Stritar[13] boiled the solution of alcohol with hydriodic acid, thus converting the ethyl alcohol into ethyl iodide, and then distilled the product. The hydriodic acid was prevented from distilling by the addition of sodium carbonate, and any free iodine was absorbed by red phosphorus. The distilled ethyl iodide was passed into silver nitrate, which decomposed it and precipitated silver iodide. From the weight of silver iodide, the amount of alcohol was calculated.

The main objections to this method are: (*a*) The reaction $C_2H_5OH + HI = C_2H_5I + H_2O$ when performed in dilute aqueous solution is not quantitative. (*b*) Extreme difficulty is encountered in trying to keep all hydriodic acid or iodine from passing into the distillate.

Schottmüller[14] precipitated the alcohol in the form of iodoform. Then he determined the amount of iodoform by weighing or by determining the iodine content.

This method must be discarded at the onset, because many other substances yield iodoform with the same treatment. We are particularly interested in a method that can be applied to distillates from human organs. Such distillates will yield iodoform even if no alcohol is present.

Group 5.—These methods depend on physical properties.

Sidersky[15] determined the alcohol by the increased miscibility of ether and water in the presence of alcohol.

Lyons[16] used the coefficient of expansion.

Haines and Marden[17] salted out the alcohol from the aqueous solution by potassium fluoride and measured it.

Kolthoff[18] uses electrical conductivity.

Lachman[19] used the relative solubility of aniline in various strengths of solutions of alcohol.

The gravity and refractometer methods have been and are used by various workers.

The methods in this group can be applied only to the determination of relatively large amounts of alcohol. They are of no use for the estimation of amounts such as are found in distillates from human organs. Since the gravity method as well as the refractometric one is used for just these purposes, we have especially studied them and will report the results below.

Group 6.—W. M. Fischer and A. Schmidt[20] have recently published a method which, they contend, gives good results. The method is as follows.

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13. Stritar: Ztschr. f. physiol. Chem. **50**:21, 1906.
14. Schottmüller: Neurol. Centralbl., 1912, no. 16.
15. Sidersky: Bull. A. chim. sucr. Dist. **27**:562, 1909.
16. Lyons: J. Am. Pharm. A. **5**:807, 1916.
17. Haines and Marden: J. Indust. & Engin. Chem. **9**:1126, 1917.
18. Kolthoff: Rec. trav. chim. **39**:126, 1920.
19. Lachman: J. Indust. & Engin. Chem. **13**:230, 1921.
20. Fischer, W. M., and Schmidt, A.: Ber. d. deutsch. chem. Gesellsch. **57**: 693, 1924; **59**:679, 1926.

The ethyl alcohol is converted into ethyl nitrite by sodium nitrite and acetic acid ($C_2H_5OH + HNO_2 \rightarrow C_2H_5NO_2 + H_2O$). The ethyl nitrite so formed is aerated at 40 C. by means of a stream of carbon dioxide into a solution of potassium iodide, acidified with hydrochloric acid. The ethyl nitrite is hydrolyzed, yielding nitrous acid ($C_2H_5NO_2 + H_2O \rightarrow C_2H_5OH + HNO_2$). The latter liberates equivalent amounts of free iodine ($2HNO_2 + 2HI \rightarrow I_2 + 2NO + 2H_2O$), which is then titrated with standard thiosulphate solution. The entire process is performed in an atmosphere of carbon dioxide. The aeration takes two and one-half hours. The authors also lay great stress on a blank determination made under exactly the same conditions and also lasting two and one-half hours. The blank determination, which in their hands amounts to 0.1 cc. of tenth normal thiosulphate, they deduct from the main determination. They claim that no substances except alcohol will respond to this test under the conditions outlined. Their results show a recovery of between 99.6 and 100.3 per cent.

Although this method necessitates the use of a complicated set of apparatus and is time-consuming, we were much impressed with it. We, therefore, gave it a thorough trial to determine whether it could be used for our purposes, namely, the estimation of small amounts of alcohol in tissue distillates. After considerable investigation, we finally decided that the method cannot be utilized, mainly because of the instability of the hydriodic acid. Blank determinations were run for one and one-half hours under exactly the same conditions as those outlined by the authors of the method. Iodine was liberated, requiring varying amounts of tenth normal thiosulphate (ranging between 12.5 and 21.3 cc.) to neutralize it. This amount of thiosulphate corresponds to 57 and 98 mg. of ethyl alcohol, respectively. As the alcoholic content in 10 cc. of tissue distillates ranges between 0.3 and 30 mg. of alcohol only, it is evident that the iodine liberated in the blank determination so much exceeds that liberated by the alcohol actually present that no quantitative results could be expected.

We next tried a series of four experiments, keeping the acidified potassium iodide solutions in the dark and at 0 C. temperature during the one and one-half hour aeration. Iodine was also liberated in these blanks. The titration of this liberated iodine yielded values corresponding to 31.2, 43.5, 62 and 73.6 mg. of alcohol. Even under these conditions, therefore, the hydriodic acid is so unstable as to yield free iodine far in excess of what a small amount of alcohol would yield.

Furthermore, in a series of blanks, results varying more than 100 per cent from each other were obtained. Without going any further into the investigation, we concluded that we had enough evidence at hand to discard the method entirely.

Preliminary experiments with the various methods outlined above resulted in the following conclusions.

Methods based on the formation of iodoform must be discarded because non-alcoholic tissue distillates yield iodoform, and those based on the production of ethyl iodide are not quantitative and are cumbersome.

Methods depending on the titration of the alcohol with a standard solution of chronic sulphuric acid were discarded because of the continued and rapid deterioration of the standards, because of the indefinite end-point and because, in tissue distillates, a great many other reducing substances are present.

Methods based on physical properties can be used only for larger concentrations of alcohol. Nevertheless, the specific gravity method and the refractometric method were studied more in detail as will be shown.

Methods depending on the oxidation of the alcohol to acetaldehyde and determining the latter colorimetrically by reduced fuchsin were also further studied.

Methods depending on the liberation of iodine by the liberated nitrous acid from the ethyl nitrite are out of the question because of the instability of the hydriodic acid.

Methods based on the oxidation of alcohol to acetic acid and titration of the latter with standard alkali seemed to us the most promising and were studied in detail.

EXPERIMENTS

At the outset, two facts must be borne in mind: First, the amount of alcohol encountered in distillates from human tissues is always less than 0.3 per cent, and differences as small as 0.05 per cent must sometimes be determined; second, in these distillates from human organs, there are always present many other volatile organic substances which may interfere in some manner.

TABLE 1.—*Amount of Distillate Required for Complete Recovery of the Alcohol*

	Distillates (Successive 100 Cc. Portions)							
	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth
Case 1.....	Positive	Positive	Positive	Slightly positive	Trace	Trace	Absent	Absent
Case 2.....	Positive	Positive	Positive	Slightly positive	Trace	Trace	Absent	Absent
Case 3.....	Positive	Positive	Positive	Slightly positive	Trace	Trace	Absent	Absent
Case 4.....	Positive	Positive	Positive	Slightly positive	Trace	Trace	Absent	Absent

The experimental work was carried out along the following lines:

1. *The Technic Necessary for the Complete Recovery of the Alcohol Present in Tissues.*—The most convenient amount of tissue used for analysis was 500 Gm. Because of the volatility of alcohol, the tissue was placed in a tightly sealed jar as soon as it was removed from the body, and kept in an icebox until the analysis was started. While ice cold, 500 Gm. was weighed and quickly ground up. This tissue pulp was placed in a 2 liter flask. To this was added 600 cc. of water, 5 cc. of a saturated solution of tartaric acid, C. P., and 1 cc. of white mineral oil. The mixture was distilled with steam, a long and well cooled condensor being used. The distillate was collected in a series of Erlenmeyer flasks, 100 cc. of the distillate being allowed to run into each flask until eight of these 100 cc. portions were obtained. The distillates were then tested for the presence of alcohol in the following manner.

About 10 cc. of the distillate from each of the eight flasks was placed in a series of eight test tubes. They were then oxidized by plunging a red hot spiral of copper into each tube ten times. The tubes were continually cooled by running water during this process. After the oxidation of the alcohol into aldehyde, 2 cc. of colorless reduced fuchsin was added to each tube and the tubes allowed to stand for five minutes. The presence of aldehyde—and, therefore, alcohol—was indicated by the development of a red color.

Tissue (liver and brain) from four persons who died while heavily intoxicated were thus examined with results shown in table 1.

It is evident that, if the distillation were continued until 600 cc. was obtained, all the alcohol would be recovered. Throughout this work, however, 800 cc. of distillate was collected in order to be sure of the complete recovery of the alcohol.

2. *Can the Alcoholic Content Be Determined by the Specific Gravity of the Distillate?*—A series of nonalcoholic brain tissues to which were added different but known amounts of alcohol were distilled by the method outlined. The quantity of alcohol added was that found in the usual type of alcoholic brains. The distillates (800 cc. portions) contained alcohol ranging from 0.003 to 0.32 per cent. The specific gravity determinations of the alcohol in these distillates gave extremely erroneous and inconsistent results. There are two main reasons why the specific gravity of these distillates cannot be expected to yield quantitative results for alcohol: First, the specific gravity at 15 C. of pure solutions of alcohol of from 0.003 to 0.32 per cent ranges between 0.99999 and 0.9994. It is obvious from this that the entire range of the alcoholic content of the distillates from human brains shows differences only in the fourth decimal place. Brain distillates having the lowest alcoholic content and those having the highest differ by a specific gravity of only 0.0005. This small value lies well within the experimental error. Second, it must be remembered that these distillates from tissues contain many other volatile substances, and these naturally affect and, hence, distort the specific gravity, due to the alcohol itself. After many series of experiments, it was finally decided that the specific gravity cannot be used even for a rough approximation of the alcoholic content of tissue.

TABLE 2.—*Refraction not Proportional to Alcoholic Content*

Case	Alcohol Content, Percentage	Refraction
1	None	1.3312
2	None	1.3310
3	None	1.3313
4	0.02	1.3310
5	0.10	1.3314
6	0.15	1.3312
7	0.15	1.3314
8	0.20	1.3315
9	0.25	1.3314
10	0.30	1.3313

3. *Can the Alcoholic Content Be Determined by the Refraction of the Distillate?*—Portions of brain tissue weighing 500 Gm. each were taken in thirty cases. They were all hospital cases, and no alcohol had been administered for at least ten days previous to death. To these portions of brain tissue, known amounts of alcohol were added. The amounts added were within the range found in alcoholic cases. They were distilled in the usual manner, as outlined above. In each case 800 cc. of distillate was collected and the refraction determined at 20 C. by the Abbe refractometer. Inconsistent results were obtained. The reason for this is that other volatile substances are present in tissue distillates. These have refractive powers of their own and, hence, distort appreciably the minute refractive increase due to the small amount of alcohol present. To illustrate this contention, results in ten of the cases are given in table 2. This method cannot, therefore, be used for the quantitative determination of alcohol in tissue.

4. *Can the Alcoholic Content Be Determined by Oxidizing the Ethyl Alcohol to Acetaldehyde and Quantitatively Determining the Latter?*—Brain material weighing 500 Gm. from a patient who died during alcoholic intoxication was treated and distilled in the manner described previously. Eight hundred cubic centimeters of distillate was collected and divided into eight 100 cc. portions.

Each portion was oxidized by sulphuric acid and successively increasing amounts of potassium dichromate at room temperature, and then distilled until 50 cc. was obtained. This second distillate was tested for acetaldehyde by reduced fuchsin and for acetic acid by titrating the acidity with twentieth normal alkali. The results are indicated in table 3.

It is evident from the results in table 3 that acetic acid is produced even with a small amount of dichromate. When enough dichromate is present to give the maximum yield of aldehyde, the acetic acid produced becomes considerable. As large amounts of acetic acid are produced even under the best conditions for aldehyde formation, this method was abandoned.

5. *Can the Quantity of Alcohol Be Determined by Oxidizing It to Acetic Acid and Then Titrating the Amount of Acid Produced?*—Numerous series of experiments along this line were tried. At first, many inconsistent results were obtained,

TABLE 3.—*A Study of Aldehyde and Acetic Acid Production by Oxidation of Alcohol*

Cc. of First Distillate Used	Cc. Sulphuric Acid (Concentrated) Added	Cc. of Saturated Potassium Dichromate Solution Added	Cc. of Second Distillate Collected	Color Obtained from 5 Cc. Distillate Plus 0.5 Cc. Reduced Fuchsin Reagent	Cc. of Twentieth Normal Acetic Acid Obtained from 45 Cc.
100	20	0.5	50	Trace	Negative
100	20	1.0	50	Trace	Negative
100	20	1.5	50	+	1.8
100	20	2.0	50	++	3.1
100	20	2.5	50	+++	7.8
100	20	3.0	50	++++	19.0
100	20	5.0	50	+++	37.2
100	20	7.5	50	++	52.5

mainly because: (*a*) Sulphur trioxide passed into the distillate, together with the acetic acid. This was finally avoided by distilling at a slow and regular rate and by using a Hopkins distilling head. (*b*) All of the alcohol was not oxidized to acetic acid. If underoxidized, some was distilled over as ethyl aldehyde, while, if overoxidized, an appreciable amount of the alcohol was converted into carbon dioxide. Both of these sources of error were finally minimized to a reasonable but constant extent by using proper proportions of sulphuric acid and potassium dichromate.

Twenty grams of potassium dichromate, 300 cc. of water and 40 cc. of concentrated sulphuric acid were placed in a 500 cc. distilling flask, and well mixed until all the dichromate had dissolved. Various but known quantities of alcohol were then added, as indicated in table 4. The distilling flask was then quickly connected to a long, well cooled condensor by means of a Hopkins distilling head. The distillation was carried out at a slow and regular rate, so that it took from forty-five to fifty minutes until exactly 250 cc. of distillate was obtained. It was definitely established by experiments that the maximum amount of acetic acid could always be recovered within this 250 cc. of distillate. Fifty cubic centimeters (one fifth) of the well mixed distillate was titrated with twentieth normal sodium hydroxide solution using phenolphthalein as an indicator. From the titration figure, the amount of alcohol was calculated (1 cc. of twentieth normal sodium hydroxide corresponds to 2.3 mg. of ethyl alcohol). The results obtained by this method are tabulated (table 4).

Repeated experiments of this sort yielded consistent results. The percentage of alcohol recovered was always between 84.6 and 86.7 per cent (average of 85.67 ± 1.02 per cent). Therefore, if the amount of alcohol found is multiplied by 1.167, the total amount of alcohol present is obtained.

It might be well to point out here how little a deviation between 84.65 and 86.7 per cent actually affects the quantitative determination of such dilute alcohol solutions. If a 0.35 per cent solution of alcohol were analyzed, we would obtain by the foregoing method (yield between 84.65 and 86.7 per cent) some value lying between 0.296 and 0.303 per cent; calculating this to 100 per cent yield we would get 0.345 to 0.354 per cent as the alcoholic content of the solution which actually contains 0.35 per cent of alcohol (an error of only 0.005 per cent).

Because of the favorable results obtained by this method, it was next deemed advisable to apply it to the determination of alcohol in the tissues. The first phase of the work consisted in finding how much titratable acidity would be obtained from alcohol-free tissue, proceeding along the method prescribed above.

TABLE 4.—*Determination of Alcoholic Content by Oxidizing It to Acetic Acid*

Gm. of Potassium Dichromate	Cc. of Water Added	Cc. of Sulphuric Acid Added	Mg. of Ethyl Alcohol Added	Cc. of Distillate Collected	Cc. of Twentieth Normal Alkali to Neutralize 50 Cc. Distillate	Mg. of Ethyl Alcohol Recovered	Percentage of Alcohol Recovered
20	300	40	None	250	0.22	—	—
20	300	40	None	250	0.20	—	—
20	300	40	None	250	0.20	—	—
20	300	40	196.2	250	15.00	170.1	86.70
20	300	40	392.5	250	29.64	338.5	86.24
20	300	40	588.7	250	44.48	508.9	86.45
20	300	40	785.0	250	59.08	677.1	86.25
20	300	40	981.2	250	72.68	833.5	84.94
20	300	40	1177.5	250	86.88	996.8	84.65

Portions of brain tissue weighing 500 Gm. from ten different persons, who had received no alcohol for at least two weeks previous to death, were distilled in the usual way as previously described. Eight hundred cubic centimeters of distillate was collected, and 300 cc. of this was oxidized and distilled according to the method outlined above. Two hundred and fifty cubic centimeters of this oxidized distillate was collected, of which 50 cc. was titrated for acidity with twentieth normal sodium hydroxide, using phenolphthalein indicator. The acidity (twentieth normal) found in 50 cc. portions of these distillates was as follows: 1.64, 1.10, 0.94, 1.30, 1.70, 1.50, 1.14, 1.70, 1.40 and 1.10 cc. These figures indicate that the acidity produced by a uniform oxidation of the substances found in human brain distillates runs remarkably parallel. The average found in 50 cc. of the oxidized distillate was 1.32 cc. of twentieth normal acidity. The greatest variation from this average in any of the cases is not more than 0.38 cc., twentieth normal. This means that from the actual acidity obtained from the oxidation of ethyl alcohol to acetic acid, 1.32 cc. twentieth normal must be subtracted to get the true values.

The second phase of the work consisted in adding small but known amounts of alcohol to each of a series of 500 Gm. brain portions. Care was taken to utilize only tissue which was positively alcohol-free. These specimens were then analyzed as already outlined. Some of the results are given in table 5.

The figures in table 5 indicate that the average recovery is 85.2 per cent, which is close to the average recovery of 85.67 per cent in pure alcoholic solutions. The variation in the percentage recovered is not enough to have any appreciable

effect on the accuracy of the method. It would be an error of only ± 0.005 per cent. As the average percentage recovered is 85.67, to obtain the total amount of alcohol present one must multiply the amount recovered by the constant 1.167.

All of the foregoing experimental evidence was conclusive enough to warrant the use of this method in the determination of the alcoholic content of human brain tissue.

THE METHOD IN DETAIL

The tissue, as soon as it is removed from the body, should be placed in a tightly closed jar and placed in a refrigerator. When ice cold, 500 Gm. is weighed out, quickly ground up and placed in a 2 liter flask. To this are added 600 cc. of water, 5 cc. of a saturated solution of tartaric acid and 1 cc. of white mineral oil. This mixture is now distilled with steam. A long, well cooled condensor should be used, and the distillation should be continued until exactly 800 cc. has been collected. The distillate is well mixed and used in the following procedure.

TABLE 5.—*Determination of Alcohol in Brain Tissue by the Oxidation and Titration Method*

	Mg. of Alcohol Added to 500 Gm. of Tissue	Twentieth Normal Acidity in 50 Cc. of Oxidized Distillate	Mg. of Alcohol Recovered*	Percentage of Recovery
1	294.4	9.35	247.1	83.9
2	294.4	9.80	245.2	83.3
3	785.0	23.05	667.2	85.0
4	785.0	23.20	671.5	85.5
5	1177.5	34.10	1005.1	85.4
6	1177.5	34.30	1011.2	85.9
7	1766.3	51.00	1524.0	86.3
8	1766.3	50.80	1517.9	86.0

* These values were calculated from the titration figure (1 cc. twentieth normal acidity = 2.3 mg. of ethyl alcohol) after subtracting 1.32 cc. twentieth normal as a constant, for the acidity obtained from nonalcoholic brain tissue.

Twenty grams of potassium bichromate and 40 cc. of concentrated sulphuric acid are placed in a 500 cc. distilling flask. Three hundred cubic centimeters of the distillate obtained above is now added and the contents mixed well. The flask is then connected to a long, well cooled condensor by means of a Hopkins distilling head, and the distillation started. The heat must be so regulated that it will take from forty-five to fifty minutes to collect exactly 250 cc. of distillate. After thoroughly mixing, 50 cc. of this distillate is titrated with twentieth normal sodium hydroxide solution, using phenolphthalein as an indicator. From this titration figure, the amount of alcohol present in 1 kilogram of brain tissue can be easily calculated as follows: (cc. twentieth normal alkali — 1.32) × 71.58 = mg. C_2H_5OH per kilogram of tissue. The figure (— 1.32) holds only for brain tissue. For other tissues, one must must determine experimentally the corresponding blank.

SUMMARY

1. The various quantitative methods for small amounts of ethyl alcohol have been studied and are discussed.

2. A quantitative method based on the oxidation of ethyl alcohol to acetic acid has been developed and is recommended.

3. This method has been successfully applied to the determination of alcohol in tissues.

4. The method gives more accurate results than any of the others on record.

General Review

THE PARASITOLOGY OF THE TUBERCLE BACILLUS*

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One cannot approach the life of the tubercle bacillus within the animal body without a thought akin to that expressed by Dante in the introductory verse to his "Purgatorio":

> I enter and I see thee in the gloom
> Of the long aisles
> And strive to make my steps keep pace with thine

It seems certain that tubercle bacilli enter the body mainly from certain of its surfaces, especially from the mucous linings of the respiratory, alimentary and conjunctival systems, without apparent abrasion of these. Since the bacillus has no locomotion of its own, it is likely that the transfer from the unbroken surface to within the body is accomplished by a carrier, and this is probably one of the wandering phagocytic cells. It is of little importance which of the phagocytic cells thus operates, as long as it is an intracellular transportation. It may be that the carrier has an influence on the future of the bacillus inside the body; that is, a polymorphonuclear cell may influence it in one way and a monocyte in another. It is also possible that any carrier may transport the bacillus to the inside of the body and there disgorge it still alive so that it may later find its disease-producing environment.

Since the tubercle bacillus comes from outside the body, it is possible either that a cycle of its existence takes place there of which we have at the present time little or no knowledge, or that its persistence is dependent on a relatively rapid transfer from host to host. Tubercle bacilli are supposed to exist outside the body for a comparatively short time and only in the discharges of an infected animal. They are thus described as true parasites. They are readily grown on artificial mediums in the test tube as a rod form, but may have a wide distribution in nature in forms unknown to us. This is suggested by the frequency with which sporelike granules occur in the test tube and in caseous material and branching forms appear in cultures; also from a study of the natural infection in cattle in which, even though controlled by segregation of nontuberculous

* From the Hygienic Laboratory, United States Public Health Service.

cattle, there constantly occurs about 1 per cent of infected animals in carefully guarded herds. While such infection may always come from the rod form, a reason exists for a careful consideration of the question of extracorporeal existence in some other form.

Von Behring early suggested an origin for the tubercle bacillus of animals, especially of the ox and man, by the constant entrance of the timothy grass bacillus into the body of the ox with its food, the adaptation of this bacillus to its new environment and the attainment finally of an ability to produce disease; following this, by passage and adaptation, a type of bacillus evolved capable of causing disease in man through the use of the milk of the cow. Such a suggestion has never met with great favor, and the attempt to raise any of the nonpathogenic acid-fast organisms to pathogenic types has met with failure. Calmette [1] discusses this subject in a recent article in the *American Review of Tuberculosis.*

The attempt to degrade the pathogenic forms has had less attention paid to it. Certainly these forms often lose their virulence in vitro culture. Virulence is a term poorly understood and is used in explanation of observed phenomena in a measure to cover our ignorance. The fact remains that by long cultivation on various artificial mediums an organism loses its power of producing disease in various animals. This may be only the survival of strains adapted to their environment. Each culture that we obtain from animal infection may be a mixture of more than one strain. Work on this phase lately carried on at the Hygienic Laboratory would indicate that degradation and change of form at least is possibly simpler than increasing the virulence of nonpathogenic forms which probably take a much longer time for selection and adaptation.

Tubercle bacilli, that is, those organisms capable of producing tubercles in animals, are divided into several types determined in classification by their ability to produce tubercles in different animals—types, for example, such as human, bovine, equine, avian, turtle, etc. Between the well marked examples of each type are all grades, even those that cannot be classified and those cultures that are obviously composed of two well defined types.[2]

The acid-fast characteristic of this group has so dominated the practice and thought of laboratory workers for the past quarter of a century that little progress has been made in the study of their biology. Much work has been done on the chemical analysis of the bacilli, on their differentiation by virulence tests, acid production and growth appearance,

1. Calmette, A.: Am. Rev. Tuberc. **12**:355, 1925.

2. Griffiith, A. S.: Brit. Roy. Rep., n. s. **88**:115; Final Report, R. C. T., App. **3**:116, 1914. Kossel, H.: Deutsche med. Wchnschr. **37**:1972, 1911.

but little attention has been paid to interpretation of the acid-fast group by technic suggested by advances along other lines in bacteriology.

Many observations have been recorded, for example, on the granules and beaded forms of the organism. Comparatively little attention has been paid to these studies, and an interpretation of granules as evidence of degeneration has found its way into the literature. On the other hand, these granules have not failed to find advocates, for the suggestion that they are sporelike bodies and that the acid-fast group is definitely related to the molds and especially to actinomyces and streptothrix.[3] The latter suggestions, in the light of studies in the field of plant bacteriology and of mutants of bacteria determined by environment, come daily more and more into a field of significance.[4] It seems possible in the light of analogy that each acid-fast type may have a number, variety and location of granules determined by its environment; that these granules are in reality vital phases of the organism, and that the acid-fast portion of the bacillus is but the house or shell common to all, in which granules of specific nature are housed, just as a row of houses exactly similar may form the residences of negroes, Indians, Chinese, Latins and Caucasians. Until we burst the bonds of the acid-fast characteristics and deal with the finer parts of this organism, we shall probably remain in the haze of bacillary biology which has encompassed us for twenty-five years or more. The hope of clearing up the field will probably come from attempts to grow colonies from individual bacteria and the study of the character of the resulting growths, as was done for *Botulinus* by Miss Bengtson.[5] Work has already been started on this task in association with the National Tuberculosis Association Research Committee. While the difficulties surrounding such a technic for the slow growing tubercle bacillus are many compared with those of rapidly growing organisms, they do not seem insurmountable.

Another field in which hope is arising is in the application of advances in chemical knowledge and technic to the field of bacterial chemistry. Until recently there has been no uniform plan for such a study, and results cannot be compared. However, a plan of chemical study of bacteria has just been prepared by Treat Johnson and will appear in the *American Review of Tuberculosis* this fall. The plan outlined has already been put into operation for the study of one strain of tubercle bacillus, H37 of Saranac Lake, which has been grown in large quantities by two different manufacturing houses on a synthetic medium devised by Long.[6]

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3. Foulerton, A. G. R.: Lancet **178**:551, 626, 769 and 802, 1910.
4. Mellon, R.: J. Bact. **10**:481, 1925; **11**:229, 1926.
5. Bengston, Ida: U. S. P. H. S. Hyg. Lab. Bull., no. 136, 1924.
6. Long, E. R.: Tubercle **6**:128, 1924.

The glassware and chemicals for this work were purchased at one time so that varying compositions should not cause variation in the bacilli or the medium. After growth at the manufacturing plant, the chemist carries out there the first stages of the chemical analysis preparatory to studying some definite substance in the organism. This may be its proteins, its lipoids or its carbohydrates. As a result of such cooperation, it is hoped that a base line will be fixed with an exact description of methods for one type of organism to be followed by a similar procedure for other types the results of which will be comparable.

Already the knowledge derived from this study has been of value and importance: for example, the observation, for the first time, of methyl cytosine in the nucleic acids in the tubercle bacillus,[7] the discovery that the sulphur mechanism has a lower or different place in the tubercle bacillus as compared with its place in many other living tissues,[8] and that the cold water soluble fraction of the organism is of growing significance.[9]

COOPERATION IN RESEARCH

A word here on the plan of cooperative research of the National Tuberculosis Association may not be out of order. For the first time there has been brought about, on a common plan, a cooperation of those best fitted to undertake these studies.[10] This would scarcely be possible were it not for the help given by the manufacturing chemists who keep furnishing constant large supplies of pure material for the use of chemists and biologists.

A base line in the chemistry of one organism could not be drawn today when knowledge has so far exceeded the capacity of an individual brain were it not for the cooperation of a large group of specially skilled men. And yet a base line is essential to the chemical comparison not only of this bacterial family but of bacterial life. The present plan of cooperation includes the Hygienic Laboratory of the U. S. Public Health Service, the Bureau of Animal Industry, the National Tuberculosis Association and the manufacturing drug houses; but, more important than these, it includes a group of skilled scientists who take different phases of the problem for study, and who meet to discuss the meaning of their results in relation with those found by other investigators.

It is too soon even to review the accomplishments of this research, but, in addition to the results noted above, an observation of more practical value has shown that the substance, lately purified and crystal-

7. Johnson, T. B.: J. Am. Chem. Soc. **47**:2838, 1925.
8. White, Smith and Sullivan: Am. Rev. Tuberc. **13**:77, 1926.
9. Johnson, T. B., to be published.
10. White, W. C.: Science, to be published.

lized by Dr. Seibert,[11] responsible for the tuberculin reaction in the medium on which the bacillus is grown, is almost similar if not identical with the water-soluble fraction which can readily be isolated in much larger quantities from the organism itself after it has been plasmolized with ether.[12] These studies would indicate also that there has been great wastage in the production of tuberculin. When one considers that the tuberculins used today are of many compositions varying in potency with almost every batch, and that we annually destroy millions of dollars worth of animals condemned by its power to give reaction, it will be seen how extremely important it is to have a purified substance that can be standardized and the reaction from which will be specific in men and animals. The bearing of these studies also on the parasitology of the tubercle bacillus in the animal body is of importance, because the changes which go on in the body may be made clearer by the influence which it is found the various pure substances separated from the organism have on living body cells.

ENTRANCE OF TUBERCLE BACILLUS INTO BODY

Let us now turn to a closer consideration of the tubercle bacillus as a parasite. We have already noted that it probably rarely gets into the body except in a carrier. If one introduces a suspension of living tubercle bacilli into the body, the bacilli disappear in various ways. They disappear very quickly from the blood stream,[13] but even here they may be found in intracellular positions for several days. It is possible that the rapid disappearance of these organisms at this stage may be by a mechanism which we must understand to enable us to cure the disease, but our knowledge will not be complete until we can arrest the process at any stage.

An interesting observation has been made by Dr. Florence Sabin and Dr. Doan [14] that in some animals there is evidence of a complete depression of the bone marrow blood manufacturing system lasting for some days after the injection of an infecting dose of tubercle bacilli. It is too soon to attempt to interpret such an outstanding observation, but Sabin, Cunningham and Doan [15] have also noted in some animals a rise of those blood cells coming from the splenolymphatic system in the first days after injecting tubercle bacilli. We know so little of the first few days

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11. Seibert, F. R.: Science **63**:619, 1926.

12. Johnson, T. B., to be published.

13. Calmette, A.: Tubercle Bacillus Infection and Tuberculosis in Man and Animals, Baltimore, Williams & Wilkins Company, 1923, pp. 245-249.

14. Sabin, F. R.: To be presented at the annual meeting of the National Tuberculosis Association, 1926.

15. Cunningham, Sabin and Doan: Bull. Johns Hopkins Hosp. **37**:231, 1925.

of natural infection that the ordinary life history of this parasite cannot fully be described.

Of the course of artificial infection we know more, for a great deal of attention has been paid to the cellular activities that result from inoculation experiments.[16] The polymorphonuclear cells in the first few days have been spoken of by many writers, and now the later observations of Sabin, Cunningham and Doan [15] that the monocyte also is busy at this time are important. The outstanding phenomenon, however, is that when tubercles become apparent as physical entities it is the epithelioid cell that is striking.

The Epithelioid Cell.—The origin and function of the progenitor of the epithelioid cell have been the cause of one of the severest battles in cytology. Beginning with the discussion between the German and French schools as to whether this cell arose from what were called the fixed connective tissue cells, as maintained by Baumgarten,[17] or from the blood as maintained by Metschnikoff [18] and the French school, the battle still wages. With the introduction of new names for the same family of cells, such as Rhagacine cell, resting wandering cell, histiocyte and reticuloendothelial cell, the outlook has become more cloudy, and the battle is likely to continue for many years, because the differentiation of this cell in all its characteristics is only hindered by giving it continuously new names which describe but one of its attributes. It makes its first appearance in the chorionic villi,[19] it becomes prominent in the blood islands [20] of the two day chick embryo, but from the beginning of the blood flow a differentiation begins which becomes more and more pronounced as the embryo develops. The cells, however, soon take on definite characteristics; it is not surprising that they retain some characteristics common to all cells, since they may contain all the chemical and physical potentialities not only of its blood islet progenitor but of the primordial cells from which all the cells of a body come. The living chemistry of this cell, the epithelioid cell, however, is essential to our understanding of tuberculosis as in one stage of the tubercle parasite's life in the body this cell would seem to exercise the function of exclusive host.

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16. Krause, A. K.: Am. Rev. Tuberc. **4**:63, 1920. Krause and Willis: Tr. National Tuberc. Assn., 1924, p. 277. Nichols: Med. News **87**:638, 1905. Gardner, L.: Am. Rev. Tuberc. **6**:163, 1922. Gardner and Dworski: Am. Rev. Tuberc. **6**:782, 1922. Wallgren: Arb. a. d. path. Inst., Helsingfors **3**:139, 1911. Yersin: Ann. de l'Inst. Pasteur **2**:245, 1888.

17. Baumgarten, P.: Ueber Tuberkel und Tuberkulose, 1885; Berl. Klin. Wchnschr. **42**:1329, 1905.

18. Metschnikoff: Virchows Arch. f. path. Anat. **113**:63, 1888.

19. Evans, H.: Am. J. Physiol. **37**:243, 1915.

20. Sabin, F. R.: Contribution to Embriology, Carneg. Inst. Wash. **9**:213-262, 1920; Bull. Johns Hopkins Hosp. **34**:277-288, 1923.

Our knowledge of its specific characteristics is really large. These cells are mononuclear with an exceptional potentiality for becoming polynuclear. Large in size ranging from about 10 microns to many times this size in the form known as "giant cells," they have a highly developed attribute of extending delicate pseudopodia. Their mechanism for adsorbing indophenol blue and some allied compounds evidenced in the oxidase and allied reactions is slight, and their segregation response to certain dyes like neutral red is peculiar to themselves. Their picture after coagulation with fixatives and staining shows peculiarities with such stains as Giemsa and Pappenheim. In vitro cultures [21] they have a tendency to overgrow other cells and to exhibit many changes found also in pathologic conditions such as tuberculosis, especially the segregation of fine fat globules.[22] They maintain a high intracellular acidity.[23] They have a peculiar enzyme acting only in a neutral or weakly acid medium.[24] Probably important with regard to tuberculosis is their relation to cholesterol and lipoids as pointed out by Anitschkow.[25] From a chemical and physical standpoint, their peculiarities are probably as clearly defined as those of any other body cell.

There is evidence that they have in the body a definite round of maximum activity which is in the spleen, lymph glands, liver and lungs and parts of the bone marrow.[26] Further than this the percentage of these cells in the circulating blood is different in different animals both in numbers and qualities.[27]

COURSE OF BACILLUS IN BODY

With the knowledge that the epithelioid cell is the outstanding feature of the early formation of tubercles in the body and that the characteristics of this cell are similar to those described for the monocyte, one would expect that in the animal body tubercles would form wherever this cell has its greatest round of activity. This is actually the case, for in the spleen and lungs and lymph glands and parts of the bone marrow we have by far the greatest expression of tubercle infection, and these are the regions of greatest frequency of this type of cell. They are, however, probably found any place where blood and lymph flow and

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21. Carrel and Ebeling: J. Exper. Med. **36**:365, 1922.

22. Lewis and Webster: J. Exper. Med. **33**:349-360, 1921. Lewis, M. R.: Am. J. Path. **1**:91, 1925.

23. Rous, P.: J. Exper. Med. **41**:379-739, 1925.

24. Opie, E. L.: J. Exper. Med. **7**:316, 1905; **10**:645, 1908.

25. Anitschkow, N.: Beitr. z. path. Anat. u. z. allg. Pathol. **57**:201, 1913.

26. Lee, F. C.: J. Exper. Med. **36**:247, 1922. Bunting, C. H.: Ibid. **35**:593, 1921. Kiyono: Folia Hemat. **18**:149, 1914. McJunkin, F. A.: J. M. Res. **42**: 201, 1920. Simpson, M. E.: Ibid. **43**:77, 1922.

27. Herrel, H.: Arch. f. d. ges. Physiol. **196**:560, 1922.

where mesoblast exists, and chance may land such a tubercle bacillus laden cell in any spot, but the maximum location still corresponds with the maximum round of activity. An attempt to follow step by step the course of this parasite after landing on the surface of the body would be as follows:

1. Any phagocytic cell may transport the parasite from the surface to the interior.

2. The parasite, if carried by a monocyte, is likely to live and multiply; carried by another type of phagocyte and disgorged if it be reabsorbed by a monocyte while still viable, it is likely to live and multiply.

3. Once within the monocyte, the parasite probably finds its natural environment and begins to multiply.

4. By virtue of its symbiotic invader, the monocyte at the same time undergoes certain changes: it swells, becomes sluggish in its movement and exhibits certain physical changes such as segregation of fat and multiplication of nuclei.

5. Carrying its burden along its ordinary channels of activity, it reaches a point which it is unable to pass because either the channel is too narrow for the swollen cell or the cell itself becomes too sluggish or too sticky to move farther. This is probably what Maximow had in mind when he called it the "resting, wandering cell."

6. Shortly after it comes to rest a change in its environment occurs as shown by a clearing of the area about it, described by Kostenitsch and Wolkow[28] and Krause,[16] which is apparent under the microscope. This clearing results probably from an exudate from neighboring vessels caused by change in the reaction or p_H value of the area in which the cell has stopped.

Such a resting place with its resulting environment of exudate is probably the beginning of a tubercle. We have no definite proof of the steps of the process, but the tubercle soon appears as a collection of cells similar to that carrying the original infecting tubercle bacilli.

As physical factors in such a collection two things are in the range of possibility; in the first place, the exudate that surrounds this cell on its coming to rest with its living freight may begin by contact with an injured cell the process of fibrillar coagulation described by Hertzler[29] Baitsell[30] and Burrows.[31] The fibrils of this coagulation may influence by thigmotaxis the arrest of other cells of the same type which pass that way in their ordinary run of activity, any one of which may become a host of tubercle bacilli disgorged from the primary cell. This phase of the tubercle formation is under study in the Osborn Zoological Laboratory at Yale. That these cells have peculiarities of adhesion due probably to differences in surface tension in what is described as

28. Kostenitsch and Wolkow: Arch de méd. expér. et d'anat. path. **4**:48, 1892.

29. Hertzler, A. E.: Pseudoperitoneum, Varicosity of the Peritoneum and Sclerosis of the Mesentery, J. A. M. A. **54**:351 (Jan. 29) 1910; Anat. Rec. **9**:83, 1915.

30. Baitsell, G.: J. Exper. Med. **23**:739, 1916.

31. Burrows: Am. J. Physiol. **77**:24 and 38, 1926.

thigmotaxis has been shown by Tait and others.[32] The problem of surface tension and adhesion may readily be a physical factor in the collection of cells in connection with tubercle formation.

The other possibility is that the primary cell with its parasitic burden may become a stimulus to multiplication of the same type of cell in the area in which it lodges by virtue of some chemical production of the combination of host and parasite. Probably both processes go on. One would expect, however, that the latter is more likely, because in later periods of the development of the tubercle there is such a distinctive zone of small lymphocytes in some animals.

It will readily be seen that it is essential that we have more knowledge of this cell, especially of its living chemistry. Sabin, Doan, Cunningham, the Lewises, Carrel, Maximow,[33] Chambers and others have widely different phases of this subject under study. Dr. Chambers'[34] work is especially interesting, for he is introducing into the substance of this and other cells not only small numbers of tubercle bacilli of various strains, but also varying fractional substances produced in the analysis of this organism at the chemical laboratory. It can scarcely be doubted that the variation of this cell in different animals, its maximum round of activity and its peculiar chemical and physical attributes have much to do not only with the location of tuberculosis in animals, but also with the question of virulence and response to different strains of the tubercle bacillus and with the chemical process that goes on in the formation of caseation and the changes that are so graphic a contrast in the uninfected and infected animal.

From the time of the gathering of these cells which form the tubercle our knowledge is limited. Some of these accumulations pass on through stages of cloudy swelling, coagulation necrosis, caseation, softening and discharge with a varying cellular response around them. Others may disappear without going through this process. The former is doubtless the course followed in the parasite's effort to pass from the host of residence to a new host.

In certain animals infected with tubercle bacilli the process apparently does not pass beyond the intracellular stage; that is, it does not proceed to coagulation necrosis and caseation. This is especially true in the rat. It is conceivable that if this infection were confined to the rat, it would die out, as the conditions for it to obtain a new host would not be fulfilled. The rat is almost equally susceptible to human, bovine and avian strains of the tubercle bacillus when these are intro-

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32. Tait: Quart. J. Exper. Physiol. **12**:1, 1918-1920. Hardy, W. B.: J. Physiol. **13**:165, 1892.

33. Maximow, A.: J. Infect. Dis. **34**:549-584, 1924.

34. Chambers, R.: J. Bact. **8**:1, 1923; J. Gen. Physiol. **8**:369-401, 1926.

duced into the peritoneal cavity. The rat infected in this way uniformly dies, but very slowly. For the first year of its existence after infection it is as well apparently as its brothers and sisters. It then begins to decline, and dies a few months earlier than its immediate relatives under the same conditions. It dies, however, not from toxemia due to the infecting organism, but probably from a species of suffocation due to packing of the lungs with enormous numbers of monocytes loaded with tubercle bacilli and fat. Lymphocytes take very little part in this process. In the terms of biology in this animal the simple phase of symbiotic existence of parasite and microscopic host is exemplified. This animal is also insusceptible to tuberculin reaction.[35] The bacillus itself is found with ease by the ordinary staining methods in enormous numbers and is seldom seen with granules. All variations are found between this simple intracellular stage of symbiosis in the rat and the more advanced extracellular conditions such as extreme caseation in man and ox and extensive fibrosis in such animals as the dog. The possibility that the failure on the part of the rat to pass on to the later phases of infection observed in other animals may be related to the observation of Anitschkow and Chalatow[36] that the rat responds differently to cholesterol than do the other animals which he used, especially the rabbit and guinea-pig.

RELATION OF LIVING CELLS OF TUBERCULOSIS TO LIPINS

No one can deal with the two living cells involved in tuberculosis, that is the epithelioid cell and the tubercle bacillus, without being struck with the relation which each has to lipins. On the one hand, of all the cells in the body the family of cells to which the epithelioid cell belongs is most concerned with the burning of fat, and the outstanding feature of the tubercle bacillus family has always been its high lipin content. The close association of these two cells with the question of lipin suggests that a survey of the present knowledge of the oxidation and reduction mechanisms used in fats is of importance as a possible factor in this disease process.

Leathes,[37] in 1909, suggested that fats are prepared in the liver for burning in the lung. Bloor,[38] in his careful studies, has shown that this process is in some way connected with the carrying potentiality of cholesterol for unsaturated fatty acids. Evans[20] and Anitschkow[26] have demonstrated that this is a function closely associated with the

35. Smith, M. I.: J. Lab. & Clin. Med. **11**:712, 1926.
36. Anitschkow and Chalatow: Centralbl. f. allg. Pathol. u. path. Anat. **24**:1, 1913.
37. Leathes, J. B.: Lancet **176**:594, 1909.
38. Bloor, W. R.: J. Biol. Chem. **59**:543, 1924.

monocyte and its cholesterol content. These observations fit in well both with what we know of the maximum round of activity of these cells and their great abundance in liver and lung and also with the seats of preference of tubercle infection in connection with them.

That the whole mechanism of cholesterol-lecithin-fatty acid is concerned in this process is further evidenced by the studies of Caldwell [39] showing the increase of cholesterol in caseous material and the decrease in lecithin. There is evidence that cholesterol and lecithin as carriers of unsaturated fatty acids balance each other in this mechanism and that the former is increased when the tuberculous process is forwarding to the stage of caseation and discharge. Cholesterol as an important factor not only in the caseation but in the primary admission of the parasite to host cell is evidenced by Mudd, Stewart and Mudd [40] who showed that the tubercle bacillus when placed at an interface between aqueous and lipoid is always drawn into the latter. Myerstein [41] has observed the value of cholesterol in counteracting the hemolytic action of soaps, and Leathes [42] has noted the remarkable action of cholesterol in diminishing the area of the monomolecular film of fatty acids, Levene [43] in his study in lysolecithine further refined our knowledge of the process. Such studies indicate that in the parasitology of the tubercle bacillus the cholesterol-lecithin-unsaturated fatty acid mechanism plays an important part—in the entrance of the bacillus to its cellular host, during its life within that host, and in its progress to caseous environment and discharge to a new host. It is therefore of especial interest that this mechanism be studied with the utmost care in tuberculosis.

In the past the lipins of the tubercle bacillus have been studied biologically only after exposure to oxidation in air, which so far as we know rapidly destroys their activity. A new series of studies by isolation in vacuo now under way with the material of the National Tuberculosis Association should open new doors to our knowledge of this important part of this organism.

There is some evidence that this mechanism in tuberculosis is largely concerned with reduction. In the course of some work in the tuberculosis research division of the Hygienic Laboratory, I found that after intravenous injection of 10 mg. of sodium telurate in aqueous solution into a rat whose lungs were well filled with monocytes filled with fat and tubercle bacilli, the rat died in about fifteen minutes; while

39. Caldwell: J. Infect. Dis. **24**:81, 1919.
40. Mudd, Stewart and Mudd: J. Exper. Med. **60**:647, 1924.
41. Myerstein: Deutsches Arch. f. klin. Med. **105**:79, 1912.
42. Leathes, J. B.: J. Physiol. **58**:6, 1923.
43. Levene, P. A.: J. Biol. Chem. **55**:743, 1923.

a control normal rat of the same weight was apparently uninfluenced by the same dose given in the same way. At necropsy and after fixation in 4 per cent formaldehyde and sectioning, the fine fat globules in the monocytes were black with reduced tellurium, and these were most abundant in the centers of the masses of cells which represent tubercles in the rat. In the normal rat there were few such black globules to be found in the sections.

Ehrlich [44] long ago pointed out the reducing capacity of the lung in connection with methylene blue injections. This type of reduction is changed in the neighborhood of a tubercle as shown by DeWitt [45] and others. It is suggested by such studies that a reduction mechanism keeping balance with an oxidation mechanism work side by side in the pulmonary circulation, and that in the cells that have to do with the reduction mechanism the tubercle bacillus mainly cohabitates.

COMMENT

It will be seen that we are unable with our present knowledge to follow step by step the chemical processes that underly the changes that go on from the grouping of bacillus laden cells that form the early tubercle through caseation to softening and discharge, nor even to define clearly the chemical processes of either parasite or host cell individually. It is suggested that they are naturally associated with a complex mechanism involving cholesterol-lecithin-unsaturated fatty acids as an oxidation-reduction system. It is likely that the results of this mechanism are different in the liver and in the lung. Liver tuberculosis is almost a negligible clinical entity while lung tuberculosis is the menace in all our clinical tuberculosis problems. There is in our present knowledge a linkage of observations that suggests this field as the richest in which to study.

There seems little likelihood of destroying all tubercle bacilli in the world. There seems, however, to be a possibility of understanding its life chemistry and that of its microscopic host, the epithelioid cell, both in its individual and in its congregate relationships, and of interfering with this relationship in a way to arrest the destructive process. Such an interference would seem to be simplest at the intracellular stage such as is found in the rat. In the future, however, we should be able to interrupt the process at any time even in the caseous period when conditions favor the parasite observation in a new host. It seems possible with work pursued along this line that we should be able with some innocuous donation to satisfy a chemical affinity that would make the

44. Ehrlich, P.: Das Sauestoff-Bedürfniss des Organismus, Berlin, 1885.

45. DeWitt, L. M.: J. Infect. Dis. **13**:378, 1913. White, Smith and Sullivan (footnote 8).

life of the parasite untenable in the body either in the cells that house it in its early stages or in the more advanced extracellular phases of its existence.

A point of view which recognizes the parasite as relentlessly pursuing its struggle for persistence as any of its macroscopic animal hosts, and finding the early environment for such persistence in one type of cell in the body that gives it protection instead of seeking to destroy it, will probably aid in advancing the understanding of this baffling disease.

Notes and News

Institute of Pathology at Western Reserve.—The General Education Board has made an appropriation to Western Reserve University of $750,000 for the construction of an Institute of Pathology. The proposed building will be situated in the Health Group of the university, in relation to the Babies' and Children's Hospital, the Maternity Hospital, the School of Medicine and the proposed new Lakeside Hospital, all connected by a tunnel system. The building as now contemplated will be 157 by 55 feet, with a basement and four floors. It will house the department of pathology and the subdepartments of clinical pathology and immunology. Research space will be provided for these and for certain of the clinical departments. In addition to the usual units for routine hospital and teaching work, there will be an amphitheater seating 135, a pathologic museum, a complete art suite and suitable animal quarters. The professor of pathology will serve as director of the institute. Plans are well under way, and it is expected that construction will start during the summer of 1927.

In addition, the General Education Board has appropriated $225,000, over the course of three years, for the general budget of the School of Medicine, Western Reserve University.

Theobald Smith Receives First Trudeau Medal.—The Trudeau Medal for 1926 of the National Tuberculosis Association was awarded at the annual meeting in Washington to Theobald Smith, Princeton, director of the department of animal pathology, Rockefeller Institute for Medical Research. Dr. Smith, in 1896, first distinguished between the bovine and the human tubercle bacilli. This is the first award of the Trudeau Medal.

Fellowships in Neuropathology.—The department of neuropathology of the graduate school of medicine, University of Pennsylvania, now includes eight fellows who are taking a three year course on fellowships donated by the Commonwealth Fund of New York. This work, which is carried out in the laboratories of the Philadelphia General Hospital, is in charge of N. W. Winkelman.

Coming Meetings.—The American Association of Pathologists and Bacteriologists will meet at the University of Rochester, N. Y., April 15 and 16, 1927. On April 14, meetings will be held by the International Association of Medical Museums, the American Association of Immunologists and the American Society for Cancer Research. The meetings of all these societies will be in conjunction with the meetings of the Federation of American Societies for Experimental Biology.

Research in Progress at the University of Minnesota.—Clarence M. Jackson, director of the department of anatomy in the University of Minnesota, has compiled a bulletin giving information about the research work at the university completed during the year ending June 30, 1925, as well as about the work in progress at the end of that year. Abstracts of each topic are given, showing briefly the purpose of the study, the methods and materials used, and the results so far as available. The bulletin gives an interesting and valuable insight into the research activities of the University of Minnesota.

National Research Council Fellowships in Medicine.—In order to receive consideration at the next meeting of the Medical Fellowship Board to be held

the latter part of April, 1927, applications for Fellowships in Medicine of the National Research Council should be filed by March 1, 1927. Applications should be addressed to the Secretary of the Medical Fellowship Board, National Research Council, twenty-first and B Streets, Washington, D. C.

Conference of Full Time Clinical Teachers.—A conference of full time clinical teachers and hospital superintendents from New York, New Haven, Baltimore, Iowa City, Rochester (N. Y.), Nashville, New Orleans and Chicago was held at the Washington University of Medicine on Nov. 29 and 30, 1926.

University News, Promotions, Resignations, Appointments.—Ferdinand C. Helwig has been appointed director of the pathologic laboratory in the Children's Mercy Hospital, Kansas City, Mo.

Ulis B. Hine, who graduated from the Indiana University School of Medicine in 1925, and then served a year as interne in the Methodist Episcopal Hospital in Indianapolis, has been appointed chief deputy coroner of Marion County in which Indianapolis is situated.

Oskar Klotz, professor of pathology, University of Toronto, has returned from Nigeria, West Africa. Dr. Klotz spent six months with the yellow fever commission of the International Health Board, at Lagos.

Charles L. Connor, instructor in pathology in Harvard Medical School, has been granted leave of absence in order to fill a temporary position as associate professor of pathology at McGill University.

Ralph M. Crumrine and James Stewart Rooney have been appointed assistants in pathology in Harvard Medical School.

In Harvard Medical School, Hugh K. Ward, formerly instructor in the department of pathology in Oxford University, England, is now instructor in the department of bacteriology and immunology, and Lawrence Weld Smith has been promoted to assistant professor in the department of pathology.

At the Boston University School of Medicine, William H. Watters, professor of pathology, has been transferred to the professorship of preventive medicine, and David L. Belding appointed professor, Charles F. Branch, assistant professor, Joseph Goldman, instructor and Julius Gottlieb, assistant, in the department of pathology and bacteriology.

Charles J. Martin, director of the Lister Institute and professor of experimental pathology in the University of London, and Sir Frederick Gowland Hopkins, professor of biochemistry in the University of Cambridge, have been appointed members of the British Medical Research Council into the vacancies caused respectively, by the death of the late Lieutenant General Sir William Leishman, F.R.S., and by the retirement of Prof. T. R. Elliott, F.R.S.

Walter M. Simpson has resigned as senior instructor in pathology in the University of Michigan, and is now instructor in surgery in the school of medicine of Johns Hopkins University.

William H. Welch has resigned the directorship of the Johns Hopkins School of Hygiene and Public Health to accept a full time chair in the history of medicine in the medical school, which has been endowed by a gift of $200,000 from the General Education Board. William H. Howell, professor of physiology and assistant director of the school, will succeed Dr. Welch as director.

Lester McGary has been appointed pathologist at the Madison General Hospital, Madison, Wis., to succeed R. McHalback, who has accepted a position in Pittsburgh.

University News, Promotions, Resignations, Appointments.—At Tulane University, New Orleans, Rodger J. B. Hibbard and S. A. Wallace have been appointed full time instructors in pathology. Members of the department of pathology in Tulane University have been appointed pathologists to hospitals in New Orleans as follows:

Hugh Lawson, New Baptist Hospital; A. V. Friedrichs, Illinois Central Hospital (succeeding M. Couret, resigned); William H. Harris, the French Hospital. The pathologists for all hospitals in New Orleans are now members of the teaching staff of the Tulane department of pathology.

At the University of Pittsburgh, Samuel A. Haythorn has resigned as professor of pathology to take up again his former position at the Singer Memorial Research Laboratory and to be associate professor of preventive medicine in the university; George R. Lacy has been promoted to professor of bacteriology and is acting head of the department of pathology and bacteriology; H. G. Little has been appointed instructor in pathology.

V. L. Andrews has resigned as pathologist to the West Penn Hospital, Pittsburgh, to accept the position of pathologist to Hollywood Hospital, Calif.

Beatrice Carrier Seegal has been appointed pathologist to the Long Island Hospital in Boston Harbor in the place of Isolde T. Zeckwer, who resigned.

Hobson Davis has been appointed instructor and Frank A. Kay associate in pathology in the school of medicine of the University of Alabama.

Irving W. Parkhurst and Adam N. Boyd have been appointed assistant resident pathologists in Vanderbilt Hospital, Nashville.

Joseph D. Wilson has been appointed assistant in pathology in Vanderbilt University and resident pathologist to St. Thomas Hospital, Nashville. The work in pathologic anatomy at Vanderbilt Hospital, St. Thomas Hospital, and the General Hospital, Nashville, is in charge of the department of pathology at Vanderbilt University.

William Adams Smith has resigned as professor of pathology in the medical school of the University of West Virginia, and is now pathologist to Veterans Hospital 79 at Outwood, Ky.

At Mt. Sinai Hospital, New York, Louis Gross, formerly of McGill University, has been appointed as acting director of laboratories; Gregory Shwartzman, bacteriologist; Michael Heidelberger, formerly of the Rockefeller Institute, chemist; Paul Klemperer, formerly of the Post-Graduate Medical School and Hospital, New York, pathologist.

Paul Brindley has been appointed adjunct professor of pathology in the school of medicine at the University of Texas.

Mickle Fellowship Awarded to Dr. and Mrs. Dick.—The University of Toronto has awarded the Charles Mickle Fellowship for the year 1926 to George F. Dick and Gladys Henry Dick for their work on scarlet fever. This fellowship, bequeathed by the late Dr. W. J. Mickle, is the annual income from an endowment of $25,000 and is awarded annually to that member of the medical profession who is considered by the Council of the Faculty of Medicine of the University of Toronto to have done most during the preceding ten years to advance sound knowledge of a practical kind in medical art or science.

Death of Karl Eberth.—Karl Eberth, aged 91, the discoverer of the typhoid bacillus in 1880, and professor of pathology in Halle from 1881 until his retirement.

Abstracts from Current Literature

Pathologic Physiology

A Classification of the Toxemias in the Latter Half of Pregnancy. H. J. Stander and C. H. Peckham, Am. J. Obst. & Gynec. **11**:583, 1926.

From a study of the records of 120 patients having toxemia in the last third of pregnancy, Stander and Peckham propose the following classification: (1) eclampsia, characterized by convulsions and other well-known symptoms in which restitution to normal occurs in the puerperium; (2) pre-eclampsia, being a mild degree of eclampsia not accompanied by convulsions; (3) chronic nephritis complicating pregnancy, in which the kidney function is incompletely restored and blood pressure during puerperium is still high; the renal dysfunction is increased with each subsequent pregnancy; (4) eclampsia superimposed on nephritis; (5) low kidney reserve, this organ being unable to cope with the added strain of pregnancy; there is a moderately increased blood pressure and a relatively small amount of albuminuria; restitution is complete, but the subsequent pregnancies may reproduce the picture.

A. J. Kobak.

The Liver as a Site of Bilirubin Formation. F. C. Mann, C. Sheard, J. L. Bollman and E. J. Baldes, Am. J. Physiol. **77**:219, 1926.

The problem of bilirubin formation in the liver is complicated by the fact that in its dual blood supply one element, the portal blood, flows in part directly from an organ which itself is the site of active bilirubin formation — the spleen — as well as by the fact that the liver is the most active site of elimination of this substance. These difficulties were overcome by removing the spleen, and preventing elimination by removal of the gallbladder and ligation of the common duct. Dogs treated in this way then had a uniform bilirubin content in all blood entering the liver identical with that of the general arterial circulation.

With this procedure there was found an altogether unexpectedly rapid rise of bilirubin following removal of the gallbladder and obstruction of the common duct. The bilirubin content of the portal blood was the same as that of the arterial blood, but in blood withdrawn from the vena cava after leaving the liver there was a definite, constant increase of bilirubin. That this was not due to temporary accumulation of bilirubin, in the liver cells, with subsequent liberation, was indicated by the constancy of the finding at all stages of the experimental procedure.

H. E. Eggers.

Insensible Perspiration: Its Relation to Human Physiology and Pathology. F. G. Benedict and H. F. Root, Arch. Int. Med. **38**:1, 1926.

Benedict and Root's excellent discussion on insensible perspiration is recommended to the reader. Their conclusions are briefly summarized here. Two methods were employed for studying the insensible perspiration. With platform scales, sensitive to 10 Gm., the insensible loss was determined over night during a period of nine or ten hours, thus enabling the calculation of the hourly loss with an accuracy of approximately 5 per cent. An extremely

sensitive balance, capable of weighing 100 Kg. with an accuracy of 0.1 Gm., has also been used for measuring this loss in successive periods of from ten to fifteen minutes' duration. Measurements by these two methods indicate that in general the larger individual has the larger insensible perspiration. Refinement in the method of measurement brought out sharply the influence of body size, ingestion of food and exercise on the insensible loss. Since these factors likewise affect the metabolism, it is evidence that there is a relationship between the insensible loss and the metabolism. Thyroid patients, whose metabolism is high, were found to have a large insensible loss, and diabetic patients, whose metabolism is low, were found to have a small loss. The relationship between the insensible perspiration and the metabolism of these two types of pathologic cases was such that when the data for the hourly insensible perspiration were plotted with reference to the twenty-four hour heat production, a straight line curve indicated the general trend of the metabolism. The ideal conditions for measuring the insensible perspiration so that the data may be used for comparative purposes require that the body should be warm and comfortable, and that the extremities, particularly in the case of women, should be well protected. This fact was brought out when it was noted that the environmental temperature, which profoundly affects the skin temperature, plays a decided rôle in the insensible loss. When the insensible perspiration of either pathologic patients or normal subjects was measured under these ideal conditions and the metabolism was determined at essentially the same time, it was demonstrated that the straight line curve based on the data for diabetic and thyroid patients may serve as an excellent index of the metabolism obtaining at the time of measurement of the insensible perspiration, even with normal subjects.

S. A. Levinson.

Edema. M. M. Kunde, Arch. Int. Med. **38**:57, 1926.

Kunde used the elastometer to determine edema. She noticed that the disappearance time for intradermally injected salt solution was normal in uncomplicated typhoid fever although temperature ranged from 99 to 104.8 F. In acute toxemias of pregnancy, the disappearance time was reduced to approximately ten minutes before edema could be detected with elastometer. In acute nephritis, disappearance time fell to thirty minutes or less before edema could be detected. In chronic nephritis with albuminuria and nitrogen retention, no edema could be demonstrated, and disappearance time for intradermally injected salt solution was normal. Edema due to cardiac decompensation disappearance time may become normal as soon as edema has subsided, as determined by the elastometer.

S. A. Levinson.

Water Metabolism. IV. Sugar Metabolism in Dehydration. E. Andrews, Arch. Int. Med. **38**:136, 1926.

Sugar metabolism in dehydration is the fourth of a series of studies on water metabolism by Andrews. Sugar metabolism as illustrated by fall in blood sugar after administration of insulin is profoundly influenced by relative degrees of hydration of animals. The intensity and duration of fall in blood sugar after administration of insulin are enormously greater in animals who are dehydrated by various means and much less in animals who are flooded with water.

S. A. Levinson.

THE UNITARY NATURE OF IMPAIRMENT OF RENAL FUNCTION. A. M. FISHBERG, Arch. Int. Med. **38**:259, 1926.

Fishberg maintains that impairment of renal function involves all the excretory functions of the kidney, regardless of the nature of the anatomic substratum and manifesting itself in the same way by lowering of the maximum concentration in which each of the individual urinary constituents can be excreted. To determine the concentration of the substance in the blood as a result of renal insufficiency the normal value of the ratio for substance is $\frac{\text{average concentration in urine}}{\text{concentration in blood}}$.

S. A. LEVINSON.

GROWTH DISTURBANCES FOLLOWING RESECTION OF JOINTS. S. L. HAAS, Arch. Surg. **13**:56, 1926.

In rabbits a careful resection of the knee joint causes practically no disturbance in the length growth of the bones. Care was taken not to injure the epiphysial cartilage plate, and at the same time to remove the whole of the articular cartilage and a thin layer of adjacent bone.

N. ENZER.

IRRADIATED ORANGE JUICE. ITS VALUE AS AN ANTIRACHITIC AGENT. H. L. MASLOW, D. H. SHELLING and BENJAMIN KRAMER, Bull. Johns Hopkins Hosp. **39**:56, 1926.

The present experiments are of a preliminary nature and serve only to demonstrate that: 1. Antirachitic properties can be imparted to orange juice by irradiation with the mercury vapor quartz lamp. 2. After the feeding of irradiated orange juice to rachitic rats, healing may be demonstrated as early as five days later and is almost complete at the end of fifteen days. Other experiments are now in progress.

AUTHORS' SUMMARY.

STUDIES IN CARBOHYRATE METABOLISM: VII. INVESTIGATIONS INTO THE TRANSFORMATION OF THE LIVER GLYCOGEN INTO GLUCOSE IN VITRO. C. LUNDSGAARD and S. A. HOLBØLL, J. Biol. Chem. **68**:475, 1926. VIII. INVESTIGATIONS INTO THE ACTION OF LIVER TISSUE AND INSULIN ON GLUCOSE IN VITRO, ibid., p. 485.

The glycogen of freshly removed, minced liver tissue kept at 37 C. in physiologic salt solution with a reaction of p_H 7.3 is transformed in vitro into alpha, beta glucose. The transformation is not influenced by the addition of insulin.

The part played by the liver in carbohydrate metabolism is to serve as an accumulation depot for glucose in the form of glycogen. The liver has no direct effect on the combustion of glucose in the organism.

ARTHUR LOCKE.

THE EFFECT OF DIHYDROXYACETONE ON INSULIN HYPOGLYCEMIA. W. R. CAMPBELL and J. HEPBURN, J. Biol. Chem. **68**:575, 1926.

No substance inconvertible into glucose, mannose or maltose can cure insulin hypoglycemia. Dihydroxyacetone does cure insulin hypoglycemia and may be a precursor of glucose.

ARTHUR LOCKE.

THE EFFECT OF HISTAMINE ON THE ACID-BASE BALANCE. A. HILLER, J. Biol. Chem. **68**:833, 1926. THE EFFECT OF HISTAMINE ON PROTEIN CATABOLISM, ibid., p. 847.

The injection of histamine into dogs in doses of 1 to 3 mg. per kilogram caused a fall of from 5 to 16.5 volumes per cent in plasma carbon dioxide and a fall of from 0.05 to 0.2 in plasma p_H. The p_H of the urine excreted after injection of histamine rose to 7.1 to 8 as compared with a value of p_H 5.4 to 6.9 before the injection.

Injections of histamine of from 1 to 8 mg. per kilogram in fasting dogs produce an increase in endogenous protein catabolism lasting for periods of several hours and proportional in intensity to the dose administered.

ARTHUR LOCKE.

RÔLE OF THE INVOLUNTARY NERVOUS SYSTEM IN INSULIN ACTION. E. F. MUELLER and H. B. CORBITT, J. Lab. & Clin. Med. **11**:823, 1926.

A deposit of insulin in the body acts by a nerve stimulation, probably of the glycogen-forming function of the liver. This nerve stimulation is conducted by way of parasympathetic fibers. The effect is active as long as the insulin deposit exists. It is stronger if the insulin deposit is made in an organ which has an especially close relationship to the involuntary nervous system, as has the skin, and if the absorption is very slow. It is weaker after deposition of the insulin in organs in which absorption takes place rapidly, for instance, the subdermal tissues, and is lacking after intravenous administration. The neural effect of insulin does not depend on the dosage of the deposit, while the hormone action in the circulation and in the body fluids does depend on the dose. Simultaneously with the beginning of the absorption from the insulin deposit and with the entrance of insulin into the circulation, the direct hormone effect is manifested. With this hormone effect and the conclusive destruction of the hormone and the elimination by natural channels, the nerve effect decreases, together with the diminution of the insulin deposit outside of the circulation, and disappears as the last part of the insulin deposit is absorbed.

S. A. LEVINSON.

EFFECT OF MUCIC ACID ON RENAL FUNCTION. W. C. ROSE and R. W. JACKSON, J. Lab. & Clin. Med. **11**:825, 1926.

Of twelve rabbits which received doses of 1 to 19 Gm. of mucic acid by mouth, four showed distinct evidence of renal involvement, as indicated by marked retention of nitrogenous waste products in the blood. The authors believe that mucic acid is scarcely a safe substance to be employed as a component of human food products.

S. A. LEVINSON.

THE INFLUENCE OF THYROID FEEDING ON THE ISLETS OF LANGERHANS IN THE GUINEA-PIG. G. R. CAMERON, J. Path. & Bact. **29**:177, 1926.

The average weight of the pancreas in grams per kilogram of the weight before thyroid feeding was commenced was 3.22 as against 2.22 Gm. in control animals, an increase of 45 per cent. The percentage of islet tissue was 1.33 as against 0.68 in the controls. The animals were fed from thirteen to sixty-three days. Sex apparently had little influence. The animals fed thyroid extract exhibited the classic symptoms of hyperthyroidism.

The author discusses various theories which have been advanced to account for islet hypertrophy in thyroid feeding. Several investigators have found an increased glycogenolytic function of the liver when thyroid was added to the diet. The author suggests that the increase in islet tissue is due partly to the excessive glycogenolysis of hyperthyroidism.

E. M. Hall.

Arthritic Muscular Atrophy: The Oxygen Consumption of Atrophied Muscles. A. E. Beryl Harding, J. Path. & Bact. **29**:189, 1926.

Working with rabbits the author found that atrophied muscles due to arthritis showed a markedly increased oxygen consumption as compared with the normal. A ratio of 8.3:4.8 was obtained. In muscles wasted as a result of disuse the oxygen consumption was unaltered. The author suggests that arthritic atrophy is due to an increased number of nerve impulses arising in the joint and rendering the spinal centers abnormally excitable. In pure disuse there is a decreased number of afferent impulses and wasting results from partial suppression of reflex excitation.

E. M. Hall.

Heredity in Acholuric Jaundice. J. M. H. Campbell and E. C. Warner, Quart. Med. **75**:357, 1926.

Acholuric jaundice in five generations in one family is reported. The condition may be inherited as a dominant mendelian character.

A Further Contribution to the Study of Congenital Porphyrinuria (Haematoporphyria Congenita). L. Mackey and A. Garrod, Quart. J. Med. **75**:357, 1926.

The chief abnormal pigment in all port wine colored urines in cases of porphyrinuria is the uroporphyrin of Fischer, from which coproporphyrin may be derived. The patients do not as a rule show any deviation from the normal in the red blood cell count or hemoglobin percentage of the blood, but the presence of immature red cells and a higher percentage of iron in the urine points to an increased destruction of red cells with a compensating abnormal production of red blood cells by the marrow. In this condition the spleen enlarges as the patient grows older, and in one case weighed 1,450 Gm. The iron reaction in both the spleen and the liver was quite marked. One of the characteristic features of this condition is the deep staining of the bones, from which the pigment may be recovered. In only two cases conspicuous pigmentation of the teeth was found. The cause of the condition lies in an abnormal sensitivity to ultraviolet rays.

N. Enzer.

Haematoporphyria Congenita (Porphyrinuria): Its Association with Hydroa Vacciniforme and Pigmentation of the Teeth. H. T. Ashby, Quart. J. Med. **75**:375, 1926.

This is a report of the second case in which pigmentation of the teeth occurred. A remarkable red coloration of the teeth was noted in a child, aged 12 months. The urine was of a port wine color since birth. Blisters and a rash appeared on the skin when it was exposed to sunlight. These took many weeks to heal. Immature red blood cells were found in the smear, but the blood count and hemoglobin percentage was normal. The bones were similarly pigmented, which could be determined by a method of transillumination.

N. Enzer.

HAEMATOPORPHYRIA CONGENITA WITH HYDROA VACCINIFORME AND HIRSUTIES. A. M. H. GRAY, Quart. J. Med. **75**:381, 1926.

Gray describes at length a case of hematoporphyria congenita, emphasizing especially the appearance of the skin. In this instance there was marked growth of hair on the face and forehead. Blisters, which on healing left small scars, formed after slight trauma or exposure to sunlight. The amount of porphyrin varied from time to time, but bore no fixed relation to the formation of the hydroa.

N. ENZER.

THE DEXTROSE TOLERANCE CURVE IN HEALTH. R. HALE-WHITE and W. PAYNE, Quart. J. Med. **75**:393, 1926.

Tests for dextrose tolerance should be made on a fasting resting subject, using 50 Gm. of dextrose. Nausea during the test causes a fall in the blood sugar, and a delay in the emptying time of the stomach delays the return of the blood sugar to the normal level. The normal fasting value is below 0.12 per cent at all ages, with an upper limit of 0.20 per cent in young adults which should return to normal in two hours. In old age the percentage is higher and the fall is slower.

N. ENZER.

EXPERIMENTAL STUDY ON TOXICITY OF EMBRYONIC EXTRACTS OF THE CHICKEN AND THEIR ACTION ON BLOOD PRESSURE. A. H. ROFFO and R. LOPEZ RAMIREZ, Bol. Inst. med. Exper. **3**:211, 1926.

Fresh extracts of chick embryos in physiologic salt solution (dilution, 30 per cent) are found to be toxic for adult fowls only during the last days of incubation; even those of from five to seven days are little effective. Hypotension and blood coagulation are produced. Elimination of the albumin by heating or filtration of the extracts makes them innocuous.

ETHEL B. PERRY.

THE CLINICAL VALUE OF THE ABDERHALDEN REACTION. L. R. GROTE, Klin. Wchnschr. **5**:971, 1926.

A study of the Abderhalden method suggests a correlation between the periodicity in the appearance of the ferments and the functional condition of the secretory glands.

ARTHUR LOCKE.

HUMAN PERSPIRATION. O. MOOG and K. BUCHHEISTER, München. med. Wchnschr. **73**:895, 1926.

The "imperceptible" sweat secretion is observed with certainty only on the hands and feet. It is decreased after the injection of atropine or epinephrine, and after venous obstruction. Pilocarpine acts antagonistically to epinephrine. Histamine has no effect. Ice held in one hand causes an increased sweat secretion on the other.

ARTHUR LOCKE.

THE INFLUENCE OF SODIUM SULPHATE SOLUTION ON LIVER DISEASE. W. ARNOLDI and R. ROUBITSCHECK, München. med. Wchnschr. **73**:1106, 1926.

The therapeutic value of the water from mineral springs (Carlsbad) is based on its capacity to diminish acidosis. The discharge of bilirubin into

the bile is facilitated and accelerated; the blood bilirubin and blood sugar values decreased, and the alkali reserve and alveolar carbon dioxide tension increased, following the drinking of such water.

ARTHUR LOCKE.

THE FATE OF INTRAVENOUSLY INJECTED SODIUM TETRAIODOPHENOLPHTHALEIN IN MAN. K. HOESCH, München. med. Wchnschr. **73**:1109, 1926.

Intravenously injected sodium tetraiodophenolphthalein is excreted through the bile passages, through the urine and through the colon. On failure of discharge of bile into the intestine, the dyestuff is gradually and almost completely eliminated through the urine.

ARTHUR LOCKE.

BIOLOGIC ACTION AND REACTION. E. A. SEEMANN, Virchows Arch. f. path. Anat. **259**:539, 1926.

Seemann indulges in a theoretical and philosophic discussion of the fundamental law of Arndt, that weak stimuli increase and stronger stimuli depress life activities. Such a diametrically opposite action is inconceivable; the explanation of the paradox lies in the universal application of the newtonian principle that action leads to reaction, but in the opposite direction. The action of stimuli is identical, but to weaker ones the reaction offered by living matter predominates; whereas with stronger stimuli the reactive force of the living matter is overcome and the action of the stimulus then alone is evident. This theoretical concept is then applied in explanation of the phenomena of inflammation, hyperplasia, immunity, neoplasia, etc.

O. T. SCHULTZ.

HEREDITY OF VON RECKLINGHAUSEN'S DISEASE. H. W. SIEMENS, Virchows Arch. f. path. Anat. **260**:234, 1926.

From the personal and anamnestic examination of the relatives of sixteen persons with von Recklinghausen's disease, Siemens concludes that this condition is not transmitted as a dominant character. Of fourteen cases with complete family records, only four were familial. A study of the pigmentary anomalies in his material led him to believe that the transmission of these also did not follow any definite genetic formula.

O. T. SCHULTZ.

EFFECT OF REMOVAL OF PITUITARY BODY. L. ARKHANGELSKY, Mediko-Biol. J. **4**:38, 1926.

After removal of the anterior lobe or the whole of the pituitary body in dogs, the animals lived for a year or more. Growth and sexual development seemed to be retarded; adiposis developed, especially about the kidneys and pelvis; carbohydrate assimilation increased as did the number of eosinophils in the blood; the suprarenals and thyroid gave evidence of increased function.

Pathologic Anatomy

INTRAPERITONEAL HEMORRHAGE COMPLICATING ABORTION. W. DOWNING, Am. J. Obst. & Gynec. **11**:503, 1926.

Vaginal bleeding was noticed in the sixth week of gestation in a secondipara, aged 32. The bleeding became progressively worse, and was associated with daily pain in the left lower quadrant. The left culdesac felt boggy and

tender. At laparotomy the peritoneal cavity contained 300 cc. of dark blood without clots. There were two subserous myomas each 2 cm. in diameter, and the uterus was enlarged to a two months' pregnancy. By pressure on the fundus and the left tube blood could be expressed through the fimbriated end. Microscopically the left tube showed no decidual tissue, but clumps of leukocytes could be seen in the mucosa near the fimbriated end, and the diagnosis was acute suppurative salpingitis. Downing believes that the bleeding was due to a back flow through the patent tube, as described by Sampson, and considers the inflammation of the tube to be secondary to the hemorrhage.

A. J. KOBAK.

SUPERNUMERARY BREAST NEAR LABIUM. J. BELL, Am. J. Obst. & Gynec. **11**:507, 1926.

A mass attached to the left labium majus by a pedicle was first noticed when the patient was 23 years old and a tertipara. It enlarged with each succeeding pregnancy (nine more), but never receded. Microscopically the tissue consisted of acini lined with cuboidal cells, surrounded by a loose connective tissue containing plasma cells. Some of the acini were dilated, and the specimen appeared to be that of a resting breast with cystic disease. This is the third case of accessory breast reported in the region of the labium.

A. J. KOBAK.

SPECIFIC LESIONS OF PERIPHERAL BLOOD VESSELS IN RHEUMATISM. WILLIAM C. VON GLAHN and ALWIN M. PAPPENHEIMER, Am. J. Path. **2**:235, 1926.

In a series of forty-seven consecutive cases of rheumatic cardiac disease, specific lesions of the small peripheral arterioles and capillaries, either systemic or pulmonary, were found in ten.

These lesions are characterized by the exudation of fibrin into and about the vessel, by destructive changes in the cellular components of the vessel wall, by a distinctive cellular reaction in the adjacent tissue and by the absence of thrombosis.

These acute lesions are followed by organization with or without formation of new collateral channels within the thickened intima and occasionally within the muscular layer.

AUTHORS' SUMMARY.

A CASE OF ADIPOSIS DOLOROSA WITH NECROPSY. N. C. FOOT, R. W. WOOD and M. C. MENARD, Am. J. Path. **2**:251, 1926.

The pituitary body was apparently at fault in this case, as in most of those that have come to necropsy. The changes in the other endocrine glands seemed to follow as a result of this. It seems reasonable to suppose that sclerosis of the thyroid, persistence of thymic tissue in a patient of 60 years and adenomas of the suprarenals could be explained on a basis of overstimulation by the hypophysis. One hesitates at speculating too broadly on this subject for fear of allowing one's conclusions to become purely metaphysical and unwarranted by the facts in hand. It is justifiable, however, to ascribe the pathologic observations in this case to a profound disturbance in the endocrine system, probably arising as a result of one of the lesions found in the hypophysis cerebri.

AUTHORS' SUMMARY.

A Study of the Process of Caseation in Tuberculosis. E. M. Medlar, Am. J. Path. **2**:275, 1926.

Caseation, cavitation and ulceration in tuberculosis appear to be due to active participation of the polymorphonuclear leukocyte in the inflammatory reaction to the tubercle bacillus. The process of caseation appears to be the same in naturally acquired tuberculous infection in fowl and man and in laboratory animals experimentally infected. The presence of the polymorphonuclear leukocyte in tuberculous inflammation is not an indication of secondary infection with pyogenic bacteria. It is an indication of the production by the growth or death of the tubercle bacillus or by the action of the tubercle bacillus on the tissue in the tubercle, or a substance which strongly attracts the polymorphonuclear leukocyte.

Author's Summary.

Gastric and Duodenal Ulcer. M. Sturtevant and L. L. Shapiro, Arch. Int. Med. **38**:41, 1926.

The question of ulcers of the stomach, particularly in relation to frequency, number, size, shape, location, color, sex and age, is important to both the clinician and the pathologist. The authors made a study of 7,700 necropsy records at the Bellevue Hospital, and it was found that gastric and duodenal ulcers taken together are less frequent than most of the published figures. Twenty-nine per cent of gastric ulcers were multiple ulcers. The longer measurement for small gastric ulcers averaged 2.35 cm. Duodenal ulcers ranged from less than 0.5 to 2 cm. in diameter. Almost any shape of gastric ulcer is possible; about 25 per cent were oval. Almost all duodenal ulcers were oval or rounded. Seventy-six per cent of gastric ulcers were found near the pylorus, 12 per cent near the cardia and 12 per cent in the midgastric zone. Nine ulcers were located on the anterior surface; three were near the pylorus. Duodenal ulcers were nearly all in the first portion of the duodenum. In seven cases of multiple ulcers the second portion was involved. Two gastric and no duodenal ulcers occurred in negroes. Gastric ulcers were found in an average of three men to one woman. Duodenal ulcers showed only a slightly greater preponderance in men. Of 7,700 necropsies, 760 were on patients who died at from 60 to 69 years of age; of these, 3.5 per cent had gastric ulcer.

S. A. Levinson.

Urinary Sediment of Normal Individuals. T. Addis, J. Clin. Investigation **2**:409, 1926.

The presence of red blood cells, white blood cells and casts in urinary sediment is generally considered pathologic. Addis, studying eighty-two specimens from seventy-four normal working medical students, found these elements in normal urine, and presents the averages and ranges of variation in their excretion within twelve hours. Collections were started at about 8:30 in the evening, the whole night urine being voided twelve hours later. No fluids of any sort were taken after breakfast of the preceding day. The average amount of urine excreted was 352 cc., with an average specific gravity of 1.031. Drops of sediment were counted in an ordinary blood counting chamber, and the following results were obtained: casts: lowest 0, highest 4,270, average 1,040; red blood cells: lowest 0, highest 425,000, average 65,750; white blood cells and small epithelial cells: lowest 32,400, highest 1,835,000, average 322,500.

M. L. Parker.

THE EFFECT OF MECHANICAL TENSION UPON THE POLARITY OF GROWING FIBROBLASTS. C. H. BUNTING and C. C. EADES, J. Exper. Med. **44**:147, 1926.

Studies of sections of tissue about sutures and healing incisions through the skin of the backs of rabbits seem to indicate that mechanical tension may determine the polarity of cell division and line of growth of developing fibroblasts, and further that a shift in tension may cause a shift in position of fibroblasts already formed.

AUTHORS' SUMMARY.

THE FUNDAMENTAL PROPERTIES OF THE FIBROBLAST AND THE MACROPHAGE. A. CARREL and A. H. EBELING, J. Exper. Med. **44**:261, 1926.

From the study of cultures of chicken fibroblasts it may be concluded that: The fibroblast is characterized not only by its morphology and staining reaction, but also by a number of physiologic properties, which become apparent in the pure cultures of the cell. There is a definite relation between the size, the number and the form of certain cytoplasmic structures, including neutral red vesicles and mitochondria, and the metabolic conditions of the fibroblast.

AUTHORS' SUMMARY.

IMPERFORATE HYMEN. A. M. FLEMING, J. Obst. & Gynec. Brit. Emp. **33**:46, 1926.

Fleming describes a membrane which completely occluded the vaginal orifice. It consisted of two covering layers of epithelium and a middle layer of connective tissue which contained some muscle fibers and appeared to be made up of two sheets. The inner epithelial covering consisted of a layer of columnar cells beneath which was a layer of stratified squamous epithelium, the superficial layers of which showed no cornification. The epithelium of the external surface was stratified squamous; the superficial layer was cornified and contained a few prickle cells. Fleming concludes that the membrane resulted from the persistence of a mass of tissue where the uterovaginal canal opens into the urogenital sinus.

A. J. KOBAK.

PATHOLOGICAL AND CHEMICAL CHANGES AND HYPEREMESIS OF PREGNANCY. A. M. DRENNAN and C. HICKS, J. Obst. & Gynec. Brit. Emp. **33**:61, 1926.

In the four cases of hyperemesis of pregnancy that Drennan and Hicks studied, they found that the toxic type had an increase in the ammonia coefficient of urine which remained high in spite of clinical improvement. One of their patients died, the liver showed central lobular necrosis and the kidney only slight changes about the glomeruli and tubules.

A. J. KOBAK.

THE PART PLAYED BY THE MEDIAN TUBERCLE IN THE MAKE-UP OF THE FACE (A STUDY OF THE HARELIP). VICTOR VEAU, Ann. d'anat. path. et d'anat. norm. méd.-chir. **3**:305, 1926.

A detailed anatomo-embryological study has been made of the so-called median tubercle. The purpose of this investigation, made by a surgeon, was the search for a rational operation for harelip.

B. M. FRIED.

THE INTERNAL CORACOCLAVICULAR LIGAMENT. H. ROUVIÈRE, Ann. d'anat. path. et d'anat. norm. méd.-chir. **3**:349, 1926.

Rouvière produces evidence to show that the internal coracoclavicular ligament originates from the fibrous transformation of two distinct muscular fascicles.

B. M. FRIED.

GAUCHER'S DISEASE: GENERAL REVIEW. CHARLES OBERLING, Ann. d'anat. path. et d'anat. norm. méd.-chir. **3**:353, 1926.

An excellent review of Gaucher's splenomegaly is given. Oberling gives a comprehensive clinical and anatomopathologic discussion on the subject, with a summary of forty-two cases from the literature. There is also an abundant bibliography.

B. M. FRIED.

THE LATENT TYPES OF PULMONARY SYPHILIS. MAURICE LETULLE and JACQUES DELSACE, Presse méd. **34**:385, 1926.

Letulle and Delsace affirm that in a number of instances syphilis affects particularly the respiratory apparatus. This can be fairly well traced only by a careful microscopic examination of the lungs.

Pulmonary lesions due to syphilis are usually polymorphous. They show, however, in a general fashion three fundamental traits: 1. Latent pulmonary syphilis has a tendency to form scattered foci or islands lost among a seemingly normal or emphysematous pulmonary parenchyma. This insular emphysema has usually an annular concentric disposition, having as its center the specific sclerotic focus. 2. The lesion due to the spirochete affects commonly a group of pulmonary lobules, forming a focus in which bronchopathies and interlobular or perilobar sclerosis will subsequently develop. Frequently the entire bronchiolic tree of a lobule shows ulcerations, or vegetations, ectasias or obliterations. Islands of honeycombed bronchiectases showing cavities filled with mucopurulent material, separated and united by bands of fibro-elastic tissue, make a striking example of a "pauci-lobular syphilitis pneumopathy." 3. Of primordial importance is the presence of subacute inflammatory nodules seen particularly within or in the vicinity of the not caseated sclerotic "lobulites" which are nothing other than inflammatory or vegetating foci. Submiliary gummatous formations, composed of lymphocytes and plasmacytes, resembling closely lymphoid follicles, can also be found in the vicinity of the altered lobules, plugging the infundibulus. The elastic armature of the marginal alveoli, which has disappeared entirely from the surface of the lobule, may be hyperplastic along the infundibular wall. The respiratory epithelium becomes a cuboidal and proliferates, thus filling the alveolar lumen.

The authors affirm that the latent forms of pulmonary syphilis are observed daily in their hospital wards.

B. M. FRIED.

SOLITARY NEOPLASM OF THE LUNG. M. GARCIA FAURE, Semana méd. **1**:617, 1926.

In Córdoba two cases of cancer of the lung were observed in the five years from 1914 to 1919, and ten in the succeeding five years when the lung cancer formed 9.7 per cent of eighty-two cases of chronic lung disease examined after death.

EARLY INFLAMMATORY REACTIONS. T. ERNST, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:229, 1926.

Ernst injected 0.2 cc. of turpentine into the subcutaneous tissues of white rats and made a morphologic study of the resulting inflammatory reaction at intervals of five, fifteen and thirty minutes, and at hourly intervals up to twenty-four hours. The most instructive microscopic preparations were obtained by means of the Unna-Pappenheim pyronin-methyl green staining method. The earliest changes noted, which were present at the end of five minutes, were slight dilatation of the vessels, swelling of some of the nuclei of the capillary endothelium and of the connective tissue, and slight edema. At the end of a half hour, the collagen fibers were swollen, nuclear changes were more marked, a few leukocytes had emigrated from the vessels, and there were present a few wandering histiocytes. The vessels contained large mononuclear cells which the author held to be endothelial in origin. The adventitial cells showed little or no change throughout the period selected for study. Mitoses were not evident during the first twenty-four hours. Basophilic staining of the cytoplasm of the stroma cells and of the endothelium was an early reaction.

O. T. SCHULTZ.

CRANIAL ANOMALY. HEDDA DIETRICH-WEINHOLDT, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:259, 1926.

In a stillborn chondrodystrophic fetus the head was greatly enlarged, the skull being divided into two portions by a ridge which separated the greatly enlarged membranous cranial portion from the deformed basal and facial portions. The synostoses of the base of the skull were ossified, the premature ossification being considered an essential factor in the causation of the anomaly and of the associated hydrocephalus. The case is compared with four previously reported examples of congenital chondrodystrophic hydrocephalus.

O. T. SCHULTZ.

COMPENSATION OF THE ARTERIAL WALL. O. RANKE, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:269, 1926.

In an article of eighty-eight pages, which contains numerous mathematical formulas and graphs and which is followed by ninety-one bibliographic references, Ranke attempts an analysis of the physical and mechanical factors operative in the arterial wall within the normal blood pressure ranges. The applicability of the three histomechanical principles by means of which Thoma had sought to explain the normal growth of the diameter, length and thickness of arteries is acknowledged, but additional factors come into play during and after the growth period, and it is on the vessel's adaptation to these that normal structure depends, whereas loss of adaptation leads to the pathologic changes resulting in atherosclerosis. Accepting Föppel's definition of elasticity, Ranke conceives the factors which are important to be distensibility (Dehnung) of the artery, the circular cross-section of the vessel, differences in elasticity or distensibility of the intima and media (Schubspannung) which tend to make these two layers glide over each other, the length of the artery, bends in the vessel which each pulse wave tends to straighten out, tonus, and branching of the vessel. The sum of all the properties of the arterial wall, dependent on the structural materials which make up the wall, which permit the artery to react normally, Ranke terms compensation, and he looks on the arteries during

youth as tubes which are fully compensated, within the limits of normal physiologic variations of blood pressure, for the various mechanical factors named above. He then applies his physicomechanical concepts to a discussion of changes which occur in arteries, using for this discussion the physiologic occlusion of the umbilical vessels and of the arteries of amputation stumps, syphilis of the aorta, and atherosclerosis. Of importance in the loss of compensation is the nutrition of the normal arterial wall; the inner two thirds of the thickness of the wall receives its nutrition from the lumen. Bends and regions of branching are naturally weak areas, because the artery wall is less fully compensated here against gliding of the intima over the media. Compensation for distensibility of the wall is complete only within physiologic limits. With the increasing blood pressure of advancing age the distensibility of the vessel wall diminishes, due to the using up of structural materials, and the diameter of the lumen increases; this senile ectasia is a physiologic process which maintains or restores the compensation of the wall. Fatty change in the intima, in agreement with Aschoff, is held to be an imbibition process. Because of the thinness of the intima during youth, fatty change causes such slight disturbance of compensation that the lesion heals and leaves no permanent alterations. But as the intima becomes physiologically thickened with advancing age, fatty change leads to disturbances of the normal union between intima and media, increases the gliding of the former over the latter, and tends to destroy the compensation for this factor. The result is fibrous proliferation of the intima which, with further fatty change and disturbed nutrition, leads to atherosclerosis. Later calcification of the atherosclerotic patches tends again to restore the compensation for gliding.

O. T. Schultz.

A Case of Aleukemic Myelosis with the Clinical Picture of Mikulicz' Disease. L. S. Hannema, Folia Haemat. **32**:116, 1926.

The parents of a boy, aged 7, first noticed an increasing swelling of the left eyelid. Later the right eyelid became swollen in a similar manner. The salivary glands and several cervical nodes were enlarged. The spleen and liver were not palpable at first, but became so later. The leukocyte count ranged from 3,200 to 7,000. The hemoglobin content and red blood cells decreased progressively. Just before death the hemogobin content was 20 per cent. First examination of the smears showed 60 per cent polymorphonuclear neutrophils, 2 per cent myeloblasts, 1 per cent myelocytes, 2 per cent undefined and 35 per cent of lymphocyte-like forms which were classified as micromyeloblasts of the type first described by Naegeli. During successive examinations this type of cell increased markedly in number. The last smears examined showed 75 per cent of these forms with only 12 per cent neutrophils. A minority of these micromyeloblasts gave a positive oxydase reaction.

At necropsy, general lymphadenopathy and enlarged spleen and liver were noted. Several leukemic foci were present in the kidneys. The lachrymal and salivary glands were diffusely and markedly enlarged. Microscopically, the normal structure of these organs was completely obliterated by round cells slightly larger than lymphocytes, some of which gave a positive oxydase reaction. These were all thought to be myeloid in origin. The author points out that the case reported by Mikulicz presented nothing clinically other than the lachrymal gland enlargement. He also mentions that this and subsequent cases

of the same type were all lymphatic aleukemias, while the present instance seems to have been definitely myelogenous. With these differences, the author asks whether the case reported is to be included as an instance of the so-called Mikulicz disease.

C. J. WATSON.

NOTEWORTHY BLOOD OBSERVATIONS IN PNEUMONIA. ANTON HITTMAIR, Folia Haemat. **32**:129, 1926.

Two cases of pneumonia are reported in which careful blood studies were made. The first, in a man, aged 28, ordinarily strong and healthy, was croupous in type. The effects were not severe, and recovery was by crisis. In this case the blood changes were marked, many young lymphoid and myeloid forms appearing during the febrile stage. Endothelial cells, young monocytes, histiocytes and irritation forms were noted. Giant neutrophils were frequently seen.

Orneth has also reported these giant neutrophils in five cases of pneumonia. Nearly all of the neutrophils showed marked toxic granulation.

The second case, that of a frail girl, aged 19, was a post-influenzal pneumonia, which progressed rapidly to death. Blood changes were scanty, consisting of toxic granulation of neutrophils, increased lobulation of monocyte nuclei and a slight increase in eosinophils.

From his observation of these two cases, the author concludes that the severity of the infection and the blood picture do not run parallel.

C. J. WATSON.

ANIMAL EXPERIMENTS WITH ROENTGEN IRRADIATION OF THE BRAIN. RUDOLF-DEMEL, Strahlentherapie **22**:333, 1926.

Studies of the brain tissue after roentgen-ray exposure have shown that hemorrhage and circumscribed degeneration occur chiefly in parts of the cerebellum while mature cells, such as glia and ganglion, do not show any changes. An acute hyperemia of the meninges, hemorrhages, edema and internal hydrocephalus are also reported to appear following heavy doses.

Demel has taken up this problem with special consideration of the secondary effect on the growth and development in young animals. Dogs 4 days old were used; the skulls were irradiated with a two-thirds skin unit dose at 25 cm. focal skin distance through 3.0 mm. aluminum four times every fifth day. Eight weeks after the last exposure a comparison of the treated animals with the untreated controls demonstrated a definite disturbance of the general development and, furthermore, ataxia; there was an atrophy of the optic nerve in the seventh week. At the necropsy, the irradiated brains were smaller and lighter in weight; chiefly the right hemisphere was atrophied; this is explained by the fact that the central ray had been directed toward the right side of the skull; the occipital lobe presented a decreased number of convolutions.

Microscopically, the pyramidal area of the medulla and several ganglions of the brain were reduced; a slight hydrocephalus on the right side had developed; the cells of the cortex showed degeneration, chiefly in the upper layers. The same changes could be observed in the ganglion cells; no inflammatory processes were present. The retina of the irradiated dogs appeared normal only near the papilla, in the periphery a complete degeneration of all layers had taken place. Further studies on mature brains will be published later.

E. A. POHLE.

EARLY HISTOLOGIC CHANGES IN SKIN THAT HAS BEEN EXPOSED TO THE ROENTGEN RAY. O. HILSNITZ, Strahlentherapie **22**:525, 1926.

It has been reported that immediately after short roentgen-ray exposures of the skin of mice, the elastic fibers were increased (Bierich). These investigations have been repeated by the author, who could not confirm the mentioned results. Areas 3 by 1 cm. on the backs of white mice were exposed to the roentgen rays, the dose varying from a 10 to a 250 (human skin unit dose) per cent skin unit dose. Immediately and twenty-four hours after the treatment the small pieces of skin were excised and prepared for microscopic examination, using Weigert's stain for elastic fibers and Mallory's hematoxylin-eosin. It appeared that the cells of the epidermis and the hair follicles showed minor changes in the size and shape of the nucleus. Sebaceous glands, blood vessels and muscles remained normal. There was no increase or any other variation in the elastic fibers.

E. A. POHLE.

CHANGES IN ARTERIES AFTER DEATH. J. PENTMAN, Virchows Arch. f. path. Anat. **259**:666, 1926.

Pentman made a study of the postmortem changes which occur in arteries. Segments of the human carotid and femoral arteries, removed shortly after death, were placed in a moist chamber and kept at room temperature or in the incubator. No attempt was made to keep the material free from bacteria. At daily intervals small portions were removed for microscopic study. The earliest change seen was pyknosis of the muscle nuclei, which became marked in forty-eight hours. Epinephrine contraction of arterial strips could be elicited in a human artery forty-eight hours after death, and in beef arteries as long as 140 hours after death. The chromotropic interstitial substance of the media showed little change for forty-eight hours, then the metachromatic reaction appeared in areas in which it had not previously been present. Collagen fibers began to swell on the third to fourth day but were still recognizable on the thirtieth day. There were no demonstrable changes in the elastic tissue during the first four days; after this time the elastic fibrils became swollen and irregular. In arteries which originally contained no lipoid material, fine lipoid droplets appeared at the poles of the muscle nuclei on the third and fourth day; in arteries which had contained lipoid material the droplets changed their position from the intima to the media and increased in size. All the changes described occurred much more quickly when the material was kept at body temperature. The author believes his results are important for an understanding of the changes which occur in arteries during life, and he thinks that the changes described may be of medicolegal importance in helping to determine the period elapsed since death.

O. T. SCHULTZ.

IMBIBITION OF VITAL DYES BY THE INTIMA OF THE AORTA. N. OKUNEFF, Virchows Arch. f. path. Anat. **259**:685, 1926.

Following the injection of trypan blue into dogs and cats Okuneff found the same patchy localization of the dye in the intima of the first portion of the aorta as his chief, Anitschkow, who is an upholder of the imbibition theory of arteriosclerosis, had described following the intravenous injection of lipoids. In other laboratory animals the staining of the intima was more diffuse. The

results were interpreted as proof of the taking up by the intima of lipoid and other materials from a tissue lymph stream which penetrates the intima from the main blood stream.

O. T. SCHULTZ.

DEPOSITION AND RESORPTION OF AMYLOID. Z. MORGENSTERN, Virchows Arch. f. path. Anat. **259**:698, 1926.

Morgenstern confirmed the work of others relating to the frequency with which amyloidosis can be caused in white mice by repeated subcutaneous injection of nutrose. In a much smaller proportion of the animals the same change may be brought about by rectal injection of the material or by overfeeding with egg or milk. The deposited amyloid material is derived from the intermediary products of protein breakdown, when protein metabolism becomes abnormal or insufficient because of excessive intake, the protein material being transformed from an emulsion to an insoluble gel in the process of deposition. The localization of the deposit occurs in those areas whose tissues are believed to function in protein metabolism, of which tissues the reticulo-endothelial system is held to be important. Typical amyloidosis could be produced in splenectomized mice. Morgenstern's experiments on the resorption of amyloid are important. Virchow had claimed that amyloid is not resorbable and remained permanently. Experimental attempts to prove or disprove this dictum have not been conclusive. Morgenstern established the presence of amyloid in his animals by the removal of small bits of the liver. The nutrose injections were then stopped and the animals killed at variable periods. Beginning disappearance of the amyloid was apparent during the latter half of the second month after cessation of the injections. Preceding this period, iodine and methyl-violet staining of the material became weaker, but the congo red staining and picrin reactions remained unchanged as long as any of the material was present. The disappearance of the amyloid was associated with the formation of a cellular granulomatous tissue in which polyblasts and giant cells were present. The complete disappearance of the amyloid required about four months. Following the completion of the resorption of the material, the cellular reaction disappeared and the tissue was restored to normal, except in the case of unusually large areas of amyloidosis, which were replaced by fibrous tissue.

O. T. SCHULTZ.

EXPERIMENTAL IODINE MYOCARDITIS. K. TAKANE, Virchows Arch. f. path. Anat. **259**:737, 1926.

Takane claims that in guinea-pigs, rabbits and white rats the continuous oral administration of small doses of organic iodine preparations (thyreiodin and sajodin) and of inorganic iodine salts (sodium iodide and potassium iodide) causes myocarditis which becomes apparent on the seventh day and marked on the twelfth day. The lesion consists of degeneration and fragmentation of the muscle fibers, with focal areas of infiltration by polymorphonuclear and mononuclear cells.

O. T. SCHULTZ.

RENAUT'S NODULES OF NERVES. D. TRETJAKOFF, Virchows Arch. f. path. Anat. **259**:743, 1926.

Tretjakoff made a histologic study of the fibrohyaline bodies present on the nerves, which were first described by Renaut as occurring on the nerves of the horse, and later found in other animals and man. Situated usually beneath

the perineurium they may vary in the amount of dense or cellular fibrous tissue which they contain. According to Tretjakoff, the common and characteristic element in all of them is a mucoid connective tissue which he terms chondroid tissue. The author considers the Renaut nodules normal elements, which are formed as the result of the functional adaptation of the nerve trunks to pressure.

O. T. Schultz.

Congenital Stenosis of Esophagus and Pylorus. A. Krokiewicz, Virchows Arch. f. path. Anat. **259**:761, 1926.

This is a report of a case of congenital stenosis of the lower orifice of the esophagus and of the pylorus associated with marked distention of the lower portion of the esophagus and of the stomach. The patient was a youth, aged 18.

O. T. Schultz.

Peri-Arteritis Nodosa. J. Baló, Virchows Arch. f. path. Anat. **259**:773, 1926.

Baló reports three cases of peri-arteritis nodosa in human beings, seen within the space of eighteen months, and one case in a dog. He paid especial attention to the lesions of the peripheral nerves. The nerve changes found were believed to be analogous to those in other tissues and to be the result of peri-arteritis nodosa of the arteries of the nerves. The occurrence of the disease in a variety of species of lower animals is reviewed. Baló concludes that the disease is a specific infectious process due to an angiotropic filtrable virus.

O. T. Schultz.

Microscopic Observations in Gingivitis Marginalis. Karl Haupl, Vrtljschr. f. Zahnheilk. **1**:1, 1925.

The paradentium — the anatomic and functional unit of gingiva, alveolar process and periodontium — is extraordinarily subject to inflammatory processes.

Marginal gingivitis causes a series of paradental inflammations, which may be designated as marginal paradentitides. Of these, alveolar pyorrhea constitutes the common, purulent exudative form. This is to be regarded as an inflammation spreading from the gingiva to the remaining paradentium, and not as a primary atrophy of the bone.

Atrophy of the alveolar process, either primary or as a secondary pressure atrophy, affords a favorable factor for the onset of marginal paradentitis. But the actual direct cause is the presence of toxic, thermal, mechanical or infectious factors, acting singly or in association with one another. Such local factors may, of course, be aided by conditions of generally lowered resistance. The cellular infiltration into the gingiva is to be viewed in part as a resorptive phenomenon, in part as one of inflammatory origin. The proliferation of epithelium and of connective tissue is an indication of altered tissue balance, working through both inflammatory and mechanical factors.

Bony atrophy takes place by a process of cellular, osteoclastic resorption, as part of the inflammatory process. It may appear early, from the most diverse of causes. Along with it may be marked alterations in cement deposition, both removal and excess deposition. The loosening of the teeth results in part from deficient regeneration of absorbed bone, in part from deficient cement deposition following damage to the cement-forming cells of the periodontium.

H. E. Eggers.

Pathologic Chemistry

LIPID EXCRETION: III. FURTHER STUDIES OF THE QUANTITATIVE RELATIONS OF THE FECAL LIPIDS. W. M. SPERRY, J. Biol. Chem. **68**:357, 1926.

The composition of the lipoids excreted by different dogs under the same conditions is uniform, although there is a variation in amount. The presence of usable fatty acids not bound to sterols suggests that the fecal lipoids enter the intestine through the walls below the absorbing portion, rather than through the bile. They may represent some sort of leakage of plasma lipoids for the purpose of lubrication of the intestine or of removal of undesirable or excess sterols from the organism.

ARTHUR LOCKE.

SURFACE TENSION AS A FACTOR IN DETOXICATION. A. R. ROSE and C. P. SHERWIN, J. Biol. Chem. **68**:565, 1926.

Surface tension is often one of the important factors entering into detoxication. But Berczeller's hypothesis, that substances toxic by virtue of their capacity to lower the surface tension of water (and thus to accumulate in high concentration at cell surfaces) are perhaps detoxified by conversion into less surface-active substances, is not entirely adequate.

ARTHUR LOCKE.

A STUDY BY MEANS OF ULTRAFILTRATION OF THE CONDITION OF SEVERAL INORGANIC CONSTITUENTS OF BLOOD SERUM IN DISEASE. J. B. PINCUS, H. A. PETERSON and B. KRAMER, J. Biol. Chem. **68**:601, 1926.

In tetany, both infantile and experimental, there is a marked decrease in the "free" calcium of the serum. In chronic nephritis, uncomplicated by uremic convulsions, the free calcium is normal. In one patient with convulsions it was definitely reduced. The phosphorus (inorganic) is invariably high in parathyroprivia tetany and in severe chronic nephritis with or without uremic convulsions. The total protein concentration of the serum in experimental and infantile tetany is about normal. Ultrafiltration of the serum at a reaction of p_H 4.7 shows that at this reaction the calcium is entirely filtrable. The failure of the calcium concentration of the serum in tetany parathyroprivia to increase after irradiation with the mercury vapor quartz lamp as it does in patients with infantile tetany makes it highly probable that infantile tetany is not a form of parathyroid tetany, and this assumption is strengthened by the absence of any increase of the inorganic phosphorus of the serum of children with tetany comparable to that found in the serum of dogs after parathyroidectomy. The fact that the free calcium of the serum may remain constant in patients with chronic nephritis even when the total calcium is definitely reduced, serves to explain why such patients do not develop convulsions.

AUTHORS' SUMMARY.

THE QUANTITATIVE ESTIMATION OF CALCIUM, MAGNESIUM, PHOSPHATE AND CARBONATE IN BONE. B. KRAMER and J. HOWLAND, J. Biol. Chem. **68**:711, 1926.

Methods are described in detail for the quantitative determination of calcium, magnesium, inorganic phosphorus and carbonate in from 0.5 to 1 mg. of bone.

ARTHUR LOCKE.

STUDIES UPON THE INORGANIC COMPOSITION OF BONES. J. HOWLAND, W. M. MARRIOTT and B. KRAMER, J. Biol. Chem. **68**:721, 1926.

Different bones of the same individual have the same inorganic composition. The ratio of calcium phosphate to calcium carbonate is greater in the normal than in the rachitic animal. This ratio varies directly with the phosphorus content of the serum.

ARTHUR LOCKE.

THE MINERAL CONTENT OF HUMAN, DOG AND RABBIT SKIN. H. BROWN, J. Biol. Chem. **68**:729, 1926.

Data are presented giving the results of determination of calcium, magnesium, sodium and potassium in the skin of man, the dog and the rabbit. Individual variability in mineral content in the same species, as well as distinct differences among different species, are pointed out.

AUTHOR'S SUMMARY.

THE ESTIMATION OF SUGAR IN BLOOD AND NORMAL URINE. S. R. BENEDICT, J. Biol. Chem. **68**:759, 1926.

This is a reply to the paper of Folin (*J. Biol. Chem.* **67**:357, 1926).

ARTHUR LOCKE.

THE CHOLESTEROL AND PHOSPHOLIPID CONTENT OF THE CUTANEOUS EPITHELIUM OF MAN. H. C. ECKSTEIN and J. J. WILE, J. Biol. Chem. **69**:181, 1926.

The cholesterol and phospholipid contents of human cutaneous epithelium vary from 13 to 24 per cent and from 2.5 to 3.15 per cent, respectively. (The subcutaneous layers contain only 0.24 per cent of cholesterol and less than 0.1 per cent of phospholipid.)

ARTHUR LOCKE.

PATHOLOGICAL VARIATIONS IN THE SERUM CALCIUM. G. H. PERCIVAL and C. P. STEWART, Quart. J. Med. **75**:235, 1926.

Applying the method of Kramer and Tisdall, they find the normal range of blood calcium to be from 9.4 to 9.9 mg. per hundred cubic centimeters of serum. Parathyroid extract does not always raise this level, is occasionally without effect and may even lower it. Its action is sometimes augmented by the addition of calcium salts. Given alone, parathyroid extract did not raise the serum calcium in a case of tetania parathyroprivia. The addition of calcium chloride caused a considerable rise. In three cases of lupus erythematosus the blood serum calcium was subnormal. In the presence of ketosis it was also found to be subnormal.

N. ENZER.

PIGMENT OF LIVER AND MYOCARDIUM. P. KÖNIG, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:181, 1926.

In a study of the microchemical reactions of the "wear and tear" (Abnutz) pigments of the liver and myocardium, König found that these give the reactions of the lipoids, but also many of those of melanin. He concludes that the pigment is not a definite chemical compound, but is composed of a nucleus of proteinogenous melanin-like material, about which are deposited lipoids freed within the cell as the result of decreased oxidation. He retains the name lipo-

fuscin for the pigment because it is so widely used in the literature, but insists that its use is justifiable only if it is understood to mean lipoid plus fuscin.

O. T. Schultz.

The Calcium-Magnesium Ratio in the Blood in Narcosis. L. Pincussen and I. N. Dimitrijevič, Klin. Wchnschr. **5**:849, 1926.

The calcium-magnesium ratio in the blood is diminished during narcosis.

Arthur Locke.

Urobilin in the New-Born. M. Winternitz, Klin. Wchnschr. **5**:988, 1926.

Urobilin is regularly found in the intestinal contents of the fetus, and the urine and stool of the new-born. This urobilin comes from the mother's blood. It is absorbed by the liver and excreted in the bile. The fetal liver posseses this excretory function as early as the seventh month, at a time when the kidneys normally have none. Bacterial urobilin formation in the intestine sets in a few hours after birth. Small quantities of urobilin are found in the serum during the fetal time and during the first days of life.

Arthur Locke.

The Ovarian Hormone and Its Clinical Use. B. Zondek, Klin. Wchnschr. **5**:1218, 1926.

The preparation, properties, dosage and titration of folliculin are extensively discussed.

Arthur Locke.

Phosphatid Lipoids of the Liver. S. Hoffheinz, Virchows Arch. f. path. Anat. **260**:493, 1926.

The Ciaccio method of mordanting tissues in a bichromate formalin mixture followed by staining of the sections with iron hematoxylin or nile blue sulphate is supposed to be a specific method for the detection of phosphatid lipoids, although its specificity has recently been questioned by Kutschera and Aichbergen. Hoffheinz investigated the method itself, studying the effect of minor variations in the different steps, and applied the method to a study of the lipoids of the liver. He concludes that the method itself yields such variable results from slight variations in technic that it is necessary for the user to permit not even slight deviation in the strength and length of action of the mordant or in the staining time, if his results are to have comparative value. He believes that the method properly carried out is specific for phosphatids or their mixtures with other lipoids, but that it does not detect any definite chemical compound. Liver cells which give no evidence of degeneration may contain small amounts of phosphatid, probably alimentary in origin. Degenerated cells may contain larger amounts deposited during life, so-called necrobiotic lipoid. After death phosphatids may also appear in the liver cells, postmortem lipoid.

O. T. Schultz.

Studies on Urea Nitrogen Concentration of the Blood: Part IV. The Effect of Guanidine and Insulin on the Blood Urea Nitrogen Concentration. Kasanu Tashiro, Tohoku J. Exper. Med. **7**:268, 1926.

When from 30 to 50 mg. of guanidine chloride per kilogram of body weight is injected into a rabbit, the blood urea nitrogen and the nonprotein nitrogen

concentration temporarily diminishes, while a larger dosage (about 150 mg. per kilogram of body weight) is followed by their gradual increase, which is still distinct even after seven hours have passed.

The subcutaneous injection of 2 units of insulin per kilogram of body weight in a rabbit gives rise to a significant reduction in the urea nitrogen and non-protein nitrogen content of the blood, comparable to that in the blood sugar. The amino acid fraction may become reduced to zero.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

COMPARISON OF THE POTENCY, POLYVALENCY AND THERAPEUTIC ACTION OF ANTI-MENINGOCOCCUS SERUMS. AUGUSTUS WADSWORTH and MARY B. KIRKBRIDE, Am. J. Hyg. **6**:507, 1926.

The agglutination test is considered the best method of standardizing anti-meningococcus serums, especially in conjunction with the use of standard cultures of the recognized groups with standard serum for comparison. Anti-serums from horses immunized with six selected strains apparently have higher titer and polyvalency than serums produced with four, twenty or sixty strains. High agglutinative activity of a serum seems in no way associated with a lack of therapeutic potency or of polyvalency, but failure of agglutination, especially with some strains, does not indicate absence of therapeutic value for the serum. In the therapeutic use of antiserums in 129 cases, a few patients reacted favorably at first but then succumbed to complicating developments. A few failed to respond at all, but on the whole, the mortality was low, and the importance of early diagnosis and prompt treatment was confirmed.

ETHEL B. PERRY.

THE EPIDEMIOLOGY OF PNEUMONIA: A STUDY OF PNEUMOCOCCUS CARRIERS AMONG FOUR GROUPS OF PERSONS OVER A PERIOD OF MONTHS. J. P. POWELL, R. M. ATWATER and LLOYD D. FELTON, Am. J. Hyg. **6**:570, 1926.

In 418 observations on ninety-three persons in four groups — high school boys, medical students, student nurses and laboratory workers — in the same city, one person developed pneumonia. This was within the limits of expectancy for that period according to the city figures for the year. Presumably every one at some time during the year becomes a carrier of a fixed type pneumococcus. Waves of prevalence of the types appear suggesting seasonal variations, differing for the several types. There seemed to be a tendency for the fixed type to disappear from the m[illegible] and throat within thirty days. Sex had no apparent influence, but within g[illegible] the distribution of types tended to be uniform. Persons in contact w[illegible] a cases carry pneumococci more frequently than other persons, but contact with carriers may also be the source. In general, there is confirmation that pneumonia appears when infection with a pathogenic form of pneumococcus and a lack of resistance in the person coincide.

ETHEL B. PERRY.

CHANCRE OF THE CERVIX WITH A REPORT OF TWO CASES. R. CRON, Am. J. Obst. & Gynec. **11**:378, 1926.

The first of Cron's two cases occurred in a patient, aged 47, who presented an enlarged cervix covered with yellowish, foul smelling slough and with numerous eroded areas. Biopsy showed only chronic inflammation and hyper-

plasia, and a panhysterectomy was performed on the suspicion of a malignancy. In sections of the cervix there was perivascular infiltration of plasma cells, and a spirochete was demonstrated by the Warthin-Starry technic. In the second case the lesion, which was situated on the anterior lip of the cervix, first appeared as a macule, three weeks after a suspicious intercourse; it later became a papule, which soon eroded and developed into a typical indurated ulcer with the same foul smelling discharge as in the first case. In both cases the Wassermann reaction became positive later.

A. J. KOBAK.

REPORT OF A CASE OF ACTINOMYCOSIS OF THE TUBES AND OVARIES. J. W. DRAPER and W. E. STUDDIFORD, JR., Am. J. Obst. & Gynec. **11**:603, 1926.

A case of actinomycosis involving the female pelvic organs secondary to gastro-intestinal infection is reported in a patient, aged 36. Vaginal examination showed the uterus to be adherently retroverted, and the adnexa felt indurated. On the first admission a posterior colpotomy was performed, releasing 6 ounces (0.19 Kg.) of yellow, foul pus, the culture of which showed only gram-negative bacilli. She was readmitted thirty-nine days later, complaining of profuse vaginal discharge, weakness and night sweats. At laparotomy there were extensive omental adhesions to the head of the cecum, which contained an abscess of yellow pus, and numerous adhesions between the small intestine at the brim of the pelvis. There was a left tubo-ovarian abscess, and the right tube was chronically inflamed. Actinomycosis was demonstrated microscopically in the left ovary, right tube and omentum, and later, at necropsy, in the numerous abscesses of the right lobe of the liver and in a subdiaphragmatic abscess which was connected with a right perirenal abscess and sinus. Actinomycotic lesions were also present in the enlarged mesenteric lymph nodes, an observation contrary to the view of some writers, who hold that actinomycosis spreads only by extension and in the later stages via the blood stream.

A. J. KOBAK.

THE HISTOPATHOLOGY OF THE SUBCUTANEOUS LESIONS IN TULAREMIA IN MAN. H. H. PERMAR and G. C. WEIL, Am. J. Path. **2**:263, 1926.

The microscopic changes of the subcutaneous lesion in human tularemia is described in detail. The lesion presents the microscopic characteristics of a granuloma.

The tissue reaction may be summarized as follows: (*a*) primary massing of endothelial cells with giant cell formation; (*b*) endothelial hyperplasia with obliteration of capillaries; (*c*) necrosis with polymorphonuclear leukocytic infiltration and liquefaction; (*d*) development of small secondary lesions which pass through the same stages and tend to fuse with the primary one, and (*e*) delayed healing by organization.

AUTHORS' SUMMARY.

THE EFFECT OF TEMPERATURE ON PROTOZOAN AND METAZOAN PARASITES AND THE APPLICATION OF INTRA-INTESTINAL THERAPY IN PARASITIC AND OTHER AFFECTIONS OF THE INTESTINE. D. DE RIVAS, Am. J. Trop. Med. **6**:47, 1926.

Experiments on protozoan and metazoan parasites demonstrate that they are rather sensitive to the action of heat as they are killed in about ten minutes at 45 C. and in a few minutes at 47 C. Colonic lavage with salt solution at from 45 to 47 C. has proved efficient and safe in the treatment of amebic dysentery and in the removal of seat worms and other parasites of the large

bowel. In a like manner warm salt solution may be applied to the duodenum by means of the duodenal tube in the treatment of Giardia infection, and in the removal of tapeworms, hookworms and other parasites of the small intestine. This method may be of use in the treatment of acute poisoning, sprue, autointoxication, etc.

E. M. HALL.

CURE OF CLONORCHIASIS BY TARTAR EMETIC. ALFRED C. REED and HARRY A. WYCKOFF, Am. J. Trop. Med. **6**:115, 1926.

The authors report a cure in a case of clonorchiasis in a Chinese woman who was excluded from this country on account of infestation with parasites of this disease. In all, four intramuscular and thirty-seven intravenous injections of a 1 per cent solution of antimony potassium tartrate were administered. The stools were free from the ova after the twenty-third injection.

E. M. HALL.

PRIMARY TUBERCULOSIS OF THE GALL-BLADDER. F. W. RANKIN and F. MASSIE, Ann. Surg. **83**:800, 1926.

In addition to the case reported, fifteen cases of tuberculosis of the gall-bladder have been reported in the literature. Not all of these were primary, some occurring in a generalized miliary infection or secondary to a well developed lesion elsewhere. Tuberculous peritonitis followed operation in the author's case.

N. ENZER.

TUBERCULOSIS OF THE CAT. A. STANLEY GRIFFITH, Comp. Path. & Therap. **39**: 71, 1926.

Analogous to other domesticated animals the cat is subjected to tuberculous infection. Moreover, Griffith's opinion is to the effect that tuberculosis of the cat is of relatively frequent occurrence. In a period of seven months he examined six dead cats which had had tuberculosis, sent to him from one veterinary clinic. Figures from other veterinary colleges in England and on the continent corroborate his statement. The present report relates the post-mortem details and bacteriologic results of thirteen cases of tuberculous cats.

All the strains isolated from the animals produced after subcutaneous infection into rabbits a rapidly fatal generalized tuberculosis, identical with that caused by tubercle bacilli of bovine origin. On artificial media the isolated bacilli showed also characteristics proper to the bovine type.

Anatomically the distribution of the lesions pointed toward the respiratory as well as to the intestinal tracts as pathways for the infection. Thus, in one instance the lungs contained a large nodule and the tributary bronchial glands were enlarged and caseating. The mesenteric glands showed no changes. In ten cases the mesenteric glands were enlarged and caseous, or caseocalcareous. In two cases, in addition to the involvement of the mesenteric glands, there was a tuberculous peritonitis. In one case tuberculosis was found in the eye. In cases in which the mesenteric glands were involved, the picture closely resembled that of tabes mesenterica, seen in human beings. In five cases Griffith found consolidation and caseation of the lungs, and in three instances cavities. The necrobiotic masses in these cases were swarming with tubercle bacilli. Tuberculosis of these three animals ought to be regarded, therefore, as an ulcerative pulmonary tuberculosis due to bovine type of the tubercle bacillus.

B. M. FRIED.

ARACHNIDISM: A STUDY IN SPIDER POISONING. EMIL BOGEN, J. A. M. A. **86**:1894, 1926.

Arachnidism, or spider bite poisoning, presents a clinical entity so striking that the diagnosis should easily be made, once the possibility is considered. One hundred and fifty cases have previously been reported in the United States, and fifteen cases have been seen at the Los Angeles General Hospital; but undoubtedly many more cases occur and may even pass unrecognized. Constant observations in this condition are a history of a bite by a black spider, followed by excruciating pain, mainly in the legs and abdomen, extreme abdominal rigidity, high blood pressure, elevation of temperature and a polymorphonuclear leukocytosis. Large doses of opiates and the application of heat are the main symptomatic remedies, but convalescent serum seems to be of specific therapeutic value.

AUTHOR'S SUMMARY.

IMPORTANCE OF SYMBIOSIS, OR CLOSE ASSOCIATION OF DIFFERENT SPECIES OF ORGANISM IN THE PRODUCTION OF CERTAIN BIOCHEMICAL PHENOMENA AND IN THE CAUSATION OF CERTAIN DISEASES AND CERTAIN SYMPTOMS OF DISEASE. ALDO CASTELLANI, J. A. M. A. **87**:15, 1926.

Symbiosis, or the close association of two or more organisms, may play an important rôle in biochemical phenomena and in the causation of certain diseases and certain symptoms of disease. Simple acid fermentation may be apparently transformed into fermentation with production of gas; for example, *B. typhosus* produces acidity, never gas, in maltose, mannitol and sorbite; *B. morgani* produces neither acidity nor gas; the association of *B. typhosus* and *B. morgani* produces acidity and gas.

It seems certain that there are diseases caused by a true symbiosis or association of two organisms, neither of which alone is capable of producing the malady. Trichomycosis rubra, trichomycosis nigra and stomatitis cryptococcobacillaris are examples of such diseases.

Certain so-called typical symptoms of diseases of which we know the specific organisms are in all probability due not to the specific germ alone but to the association of the specific germ with one or more nonspecific organisms. The moldy or mousy smell of favus is not caused directly by the fungus, but by associated organisms; the typical honey-yellow crusts of yaws seem to be caused by the pyogenic cocci associated with the specific germ, *Treponema pertenue*. The great abdominal distention in certain cases of typhoid is probably due to defective tone in the walls, but may be caused or increased to a certain extent by the association of certain bacilli, as, for instance, *B. morgani*, to the typhoid bacillus. The typhoid bacillus alone does not produce gas in any carbon compound.

AUTHOR'S SUMMARY.

STUDIES IN MICROBIC HEREDITY: VI. THE INFECTIVE AND TOXANOMIC SIGNIFICANCE OF A NEWLY DESCRIBED ASCOSPORE STAGE FOR THE FUNGI OF BLASTOMYCOSIS. RALPH R. MELLON, J. Bact. **11**:229, 1926.

Evidence is produced for the formation of four-celled asci with types I and II of the parasites of blastomycosis as described by Ricketts. This perfect stage, according to mycologists, represents a form of endosporulation not definitely observed before.

This phase of the culture's development appears in our experience exclusively in the so-called secondary colonies, although all varieties of secondary colonies

do not contain them. Associated with the asci are other forms of special viability such as the "dauernzellen," and oidia which may or may not be pigmented.

The probable occurrence of asci and related special growth forms in the tissues of the host offers plausible explanation for recrudescences of the disease after apparent cure.

Demonstration of ascus formation in the cultures suggests allocation of these organisms among the ascomycetes (endomyces) rather than with the oidia of Ricketts or the cryptococci of Vuillemin.

AUTHOR'S SUMMARY.

THE BLOOD-AGAR PLATE FOR SPORE-FORMING ANAEROBES. LUTHER THOMPSON, J. Bact. **11**:305, 1926.

The anaerobic blood-agar plate [anaerobic conditions secured by means of a novy jar exhausted with hydrogen or by combining this with the alkaline pyrogallol method] offers a good general means of isolating and cultivating spore-forming anaerobes. It is also an aid in judging the purity of cultures. Three groups of the anaerobes can be made, classified according to their effect on red blood cells: (1) the hemolytic group, comprising all of the well known pathogenic forms investigated in this work; (2) the group producing methemoglobin, or green zone colonies, and (3) that without effect on hemoglobin. The blood-agar plate offers a rapid method of judging the significance of spore-forming anaerobes which may be encountered in clinical bacteriology, since the common pathogenic forms are hemolytic. As an additional cultural method for identification of anaerobes, the blood-agar plate should be as valuable as, if not more valuable than, any one of the test media commonly employed such as brain broth, coagulated egg broth and litmus milk.

AUTHOR'S SUMMARY.

CELLOBIOSE AS AN AID IN THE DIFFERENTIATION OF MEMBERS OF THE COLON-AEROGENES GROUP OF BACTERIA. HENRY N. JONES and LOUIS E. WISE, J. Bact. **11**:359, 1926.

The results seem to indicate that the use of cellobiose affords a means of differentiating the genera Escherichia and Aerobacter that is fully equal to those now in use in dependability and superior to them in simplicity and in the ease of interpretation.

AUTHORS' SUMMARY.

STUDIES ON THE EFFECT OF CERTAIN TOXIC SUBSTANCES IN BACTERIAL CULTURES ON THE MOVEMENT OF THE INTESTINES. I. THE EFFECT OF SOLUBLE TOXIC SUBSTANCES OF YOUNG CULTURES OF BACILLUS PARATYPHOSUS B. E. E. ECKER and A. RADEMAEKERS, J. Exper. Med. **43**:785, 1926.

Following intravenous injection filtrates of young cultures of *Bacillus paratyphosus B* often produce marked diarrhea in rabbits. A study was made of the effect of these toxic filtrates on the motility of the small intestines of the rabbit. The observations were made on a segment of the small intestines in situ and in the living animal. It was found that an immediate slight rise of tone of the longitudinal muscles occurred following intravenous injection of sterile broth. The same rise was noted after the injection of the toxic filtrate; but with these it was followed later (ten minutes elapsing, at least) by a strong but gradual rise of the diastolic and systolic tone, i. e., by spasmodic contraction of

the intestinal muscle, which persisted at times for as long as two hours. In order to record simultaneously the effect on the longitudinal and circular muscles and the propulsive efficiency of the segment the Sollmann and Rademaekers modification of Baur's technic was employed. This arrangement showed that the stimulation of the longitudinal muscles is accompanied by a similarly strong stimulation of the circular muscles, by peristalsis and, therefore, by a greatly increased propulsion of intestinal contents which was sufficient to overcome the inhibition that usually occurs after preparation of the animal. With this arrangement an instance of peristaltic spasm was also noted. Broth alone failed to produce the phenomenon. Isotonic magnesium chloride or sulphate added to the bath relaxed the muscles again. Animals under deep urethane anesthesia did not show the diarrhea which occurred in the intact controls, but sometimes exhibited it after the effect of the anesthetic had disappeared. So far no effects have been observed on the isolated strip (Magnus method), and further studies are being made to localize the effect, to neutralize it with a specific antiserum and to observe the effect of filtrates of other members of the bacterial group including the dysentery bacilli.

AUTHORS' SUMMARY.

THE CULTIVATION OF THE GRANULES OF VACCINIA VIRUS. E. C. CRACIUM and E. H. OPPENHEIMER, J. Exper. Med. **43**:815, 1926.

The technic is described whereby vaccinia "granules'" are separated from all other material of glycerolated vaccinia calf lymph and cultivated in vitro with embryonic tissues.

These "granules" remain alive as tested by rabbit corneal inoculation for as long as seventy-one days, when grown in connection with growing tissue; they fail to remain potent if cultivated with dying cells, showing in this way the same characteristics as whole vaccine virus. The potency of the "granules" increases with the age of the culture under the first mentioned conditions.

The fluid part of the vaccinia lymph which remains after the removal of all "granules" is impotent under all conditions.

AUTHORS' SUMMARY.

ANATOMIC STUDY OF RABBIT SNUFFLES WITH SPECIAL REFERENCE TO ETIOLOGY, AND CORRELATION WITH EXPERIMENTAL PFEIFFER BACILLUS PNEUMONIA AND HUMAN INFLUENZAL PNEUMONIA. ASAZO TANAKA, J. Infect. Dis. **38**: 409, 1926.

The principal pathologic changes in snuffles caused by either *Bacterium lepisepticum* or *Bacillus bronchisepticus* in rabbits are rhinitis, sinusitis and, in the lung, intense engorgement, hemorrhage and edema, bronchitis, bronchopneumonia, perivascular infiltration and inflammation of the serous cavities.

Bact. lepisepticum snuffles also causes perivascular edema, bronchiectasis, congestion of the inner organs and bacteremia.

B. bronchisepticus snuffles also causes peribronchial infiltration and bronchiolitis.

The pathologic changes in rabbits having snuffles induced experimentally by intranasal inoculation with secretion of snuffles containing *Bact. lepisepticum* or *B. bronchisepticus* and by injections of pure cultures of these organisms are similar in all respects to those of the naturally acquired diseases.

The pathologic changes in snuffles pneumonia caused by *Bact. lepisepticum* or *B. bronchisepticus* are similar in many respects, with the following differ-

ences. Frequent occurrence of abscesses, suppurative inflammation, bronchopneumonia, purulent pleurisy and marked lymphangitis are most prominent in the former, while hemorrhage and edema are most marked in the latter.

The pathologic changes in *Bact. lepisepticum* pneumonia seem to be nearly identical with experimental *Bacillus influenza* pneumonia in rabbits, and also very similar to influenzal pneumonia of monkeys, except perivascular infiltration and suppurative inflammation are more marked in the *Bact. lepisepticum* pneumonia.

The characteristic changes of human influenzal pneumonia are also observed to be closely similar to *Bact. lepisepticum* pneumonia in rabbits, except that in the human disease no hyaline coagulated masses are found and perivascular infiltration is less commonly observed.

In pneumonia, *Bact. lepisepticum* may invade the lungs in two ways—either through the lymphatics or through the respiratory passages. Suppurative processes in *Bact. lepisepticum* pneumonia are probably caused by *Bact. lepisepticum.*

In test on laboratory animals with *B. influenzae* or *Bacillus pertussis,* the possible presence of *Bact. lepisepticum* or *B. bronchisepticus* in normal and infected animals must always be considered.

AUTHOR'S SUMMARY.

CYTOMORPHOSIS OF THE TUBERCLE BACILLUS AND OTHER ACID-FAST MICRO-ORGANISMS. H. J. CORPER, J. Lab. & Clin. Med. **11**:936, 1926.

Corper has shown that rapidly developing acid-fast nonpathogenic tubercle bacilli (Smegma, "Koch-Novy" and "Day") and rapidly and slowly developing pathogenic tubercle bacilli (human, bovine and avian), grown on glycerol-agar and egg mediums, undergo a regular metamorphosis-cytomorphosis which can be correlated with the time and growth curve of the bacilli. The period of early (accelerating) growth is identified with the presence of a large number of long filamentous, uniformly staining, acid-fast bacilli, while the period of adult (phase of negative acceleration) growth is identified with a preponderance of moderately long bacillary forms with and without metachromatic granules, and the senescent cells consist of uniformly acid-fast coccoid and short bacillary forms. Correlated with macroscopic observations and cultural transplant studies, for slow growing human and bovine tubercle bacilli, the young embryonic forms were evident during the active period (first few months) of macroscopic growth on glycerol-agar and egg mediums while the senescent forms predominated (after from eight to nine months), when subculturing to these mediums became more difficult or unsuccessful. The tuberculous pus resulting from the subcutaneous injection of large amounts of living or heat-killed human or bovine tubercle bacilli (from a culture six weeks old) into guinea-pigs, revealed predominantly the adult forms of tubercle bacilli. There was a gradual decrease in the number of bacilli present microscopically in the pus whether produced by living or heat-killed bacilli, until that obtained after fifty days contained only a few bacilli or was negative. During the period of observation possible, there did not seem to be any change in relations of the forms of bacilli present in the pus at the local site of injection, and the virulence of the strain seemed to play no part, although the animals infected with the virulent strains died of a generalized tuberculosis within approximately one month after infection.

S. A. LEVINSON.

INHIBITION OF BACTERIAL GROWTH BY SOME AMINO-ACIDS AND ITS BEARING ON THE USE OF TRYPTIC DIGESTS AS CULTURE MEDIA. J. GORDON and J. W. M'LEOD, J. Path. & Bact. **29**:13, 1926.

The authors investigated fourteen different amino-acids with regard to their effect on the growth of bacteria in concentrations from 0.1 to 1 per cent in 1 per cent peptone broth. The more delicately growing organisms, such as pneumococcus, streptococcus and meningococcus, were distinctly influenced by some amino-acids. On this basis the amino-acids were divided into three groups: (*a*) indifferent amino-acids—arginine, glutamic acid, l-histidine, l-leucine, d-lysine, tyrosine and valine (these are inhibitory to the pneumococcus in concentration of 1 per cent or over); (*b*) favoring amino-acids—taurine, aspartic and alamine; (*c*) inhibitory amino-acids—cystine, glycine, phenylalamine and tryptophane.

Although taurine is not strictly an amino-acid, it has a markedly favorable effect on bacterial growth; copious growth resulted even when the controls showed none.

Tryptophane, according to the authors, is the most toxic, and influenced growth with a wide variety of bacteria. They believe that the probable explanation of this toxicity is that the product resulting from deaminization is toxic. In the case of tryptophane, this substance would likely be indol. On investigation of the antiseptic properties of indol, they found it more potent than phenol. The ratio of inhibitory effect of tryptophane to phenylalamine is roughly proportional to the ratio of the antiseptic potencies of indol and phenol.

It has been found that the addition of serum to tryptic digests often causes marked increase in bacterial growth. The authors believe that the addition of serum protects the bacteria against concentrations of amino-acids which would otherwise inhibit their growth. In the absence of serum, mediums with a basis of tryptic digest are inferior to peptone broth for growing delicate bacteria. Such mediums can be improved if a considerable part of the amino-acid is removed by butyl alcohol extraction.

E. M. HALL.

HEREDITARY TRANSMISSION OF TULAREMIA INFECTION BY THE WOOD TICK. R. R. PARKER and R. R. SPENCER, Pub. Health Rep. **41**:1403, 1926.

The results of the experiments demonstrate the hereditary transmission of *Bacterium tularense* in the intermediate host, *Dermacentor andersoni*. Eight of fifteen female ticks engorged on infected hosts transmitted infection to their progeny. In two of the eight positive lines of descent, however, infection was recovered only from the eggs and was not demonstrated in the resultant larvae or nymphs. In the other six (in only three of which was egg infection demonstrated) it was recovered from the larvae or nymphs or both. In no one line of descent was it recovered from all three of these stages. Four of the five lots of eggs that gave positive tests caused typical acute infections in the guinea-pigs receiving injections of eggs. Only one lot of larvae and one of nymphs, however, caused typical acute death in their hosts. Both were from the same parent. In all other positive tests, tissue transfers from the host animals or from the guinea-pigs receiving egg or tick injections (which were apparently well when killed for necropsy) were necessary in order that the presence or apparent absence of infection might be established.

The results, as stated, suggest: (1) that not all infected females transmit infection to their progeny; (2) that the virulence of infection transmitted

may vary in the progeny of different females, even though all were infected from a common source, and (3) that in some lines of descent the infection may die out. The same apparent tendencies have been noted in the much more extensive studies of the virus of Rocky Mountain spotted fever in the same species of ticks.

The fact that in each line of descent not all stages were shown infective and that many of the positive tests were apparent only after one or more transfers from the guinea-pigs initially tested indicates the inadvisability of placing undue reliance on apparently negative tests.

The apparent failure to recover infection from the three lots of adults shown to have been infective as nymphs does not necessarily indicate absence of the infectious agent; but even if the agent were absent, the result would not detract from the significance of the positive results secured with eggs, larvae and nymphs. The data justify the conclusion that hereditary transmission occurs, but do not warrant any deduction as to the percentage of infected females that thus transmit the bacterium, or how far it will persist in the subsequent stages. These points doubtless are determined by the condition attendant on any particular test.

The hereditary transmission of *Bacterium tularense* by *Dermacentor andersoni* is of interest for two reasons: 1. Hereditary transmission of the bacterium assures a greater number of infected ticks in nature than if stage to stage transmission were confined within limits of a single generation, and it therefore becomes significant as a definite aid in the natural maintenance of infection. 2. Although the hereditary transmission of certain protozoa, of some species of rickettsiae and of symbiotic micro-organisms, by insects or arachnids is a recognized phenomenon, this paper is believed to the first record of similar transmission of a known bacterium.

AUTHORS' SUMMARY.

THE TRANSMISSION OF HUMAN PROTOZOA. R. W. HEGNER, Science **64**:28, 1926.

This article is an abstract of lectures at the London School of Hygiene and Tropical Medicine. It summarizes well the knowledge of the transmission of human protozoan parasites under the headings of intestinal, blood-inhabiting and tissue-inhabiting protozoa. The problems of relapse in malaria receive special attention on account of their bearing on transmission. Because malarial organisms will live in artificial cultures only in the presence of sugar, experiments were made on the effects of increasing and decreasing the sugar in the blood in birds with malaria. In birds receiving insulin daily the infection does not become so severe as in controls while in birds fed sugar during the hours when segmentation is going on, the number of parasites increases beyond the usual maximum for normal infections.

HYDATID CYSTS IN CHILDREN. H. MILLS, Surg. Gynec. Obst. **42**:585, 1926.

Devé, in 1918, pointed out that the seeds of echinococcosis are sown in infancy, and it is the extreme latency of the disease which is responsible for the fact that the majority of hydatid cysts cause no symptoms until the patient has attained the age of from 20 to 40 years. In children the hydatid cyst is a simple one without complications, whereas in adults it is already an old one. The proportion of suppurating cysts rises with the age of the patient. Echinococcosis is common in South America. The author reviews a large number

of cases reported from Argentina, Uruguay, Spain, Brazil, France, Australia, England, South Africa, Germany, Holland and Switzerland. In North America, only five cases of hydatid cysts in children were reported up until 1901. Since then three more cases have appeared in the literature. To these the author adds three cases, bringing the total number in children in North America to date up to only fourteen.

M. L. PARKER.

A CONTRIBUTION TO THE STUDY OF THE VIRUS OF HERPES. (MOROCCAN STRAIN.) P. REMLINGER and J. BAILLY, Ann. de l'Inst. Pasteur **40**:253, 1926.

A strain of herpes virus isolated from the lip of a Moroccan was used in a large series of animal experiments. The guinea-pig was found to be less susceptible to the disease, and the symptoms are less characteristic than those produced in rabbits. By passage the virus may become very virulent for cats, and from such a passage strain it is possible to produce the disease in dogs. In rabbits, herpes of the nervous system was produced by intradermal, epidermal, subcutaneous, intraperitoneal, intralingual, intratesticular, intravenous, intraconjunctival, intranasal inoculations and by ingestion preceded by bile feeding. The virus is found in the central nervous system and in some of the large peripheral nerves, in the saliva and exceptionally in the blood. It has not been found in the pancreas, bile, bone marrow or urine. It diffuses in glycerol and impregnates normal brain tissue. It was not found possible to detect antibodies by complement fixation. There does not appear to be any antagonism between the virus of herpes and the virus of rabies; both can develop in the same brain.

G. B. RHODES.

A CONTRIBUTION TO THE STUDY OF DISEASES PRODUCED BY FILTRABLE VIRUSES IN INSECTS. A NEW GROUP OF ULTRAMICROBIAN PARASITES: THE BORRELLINA. A. PAILLOT, Ann. de l'Inst. Pasteur **40**:314, 1926.

Several entities of silk worm infection are described and a classification made basing the etiology on a family between bacteria and protozoa which is given the name *Borrellina*. It is a filtrable group of organisms which are visible as granules with the ultramicroscrope. It occurs intracellularly in cells of mesodermic origin, particularly in adipose cells in which the nucleus is attached and the characteristic changes take place. The diseases have a relatively long incubation period and are congenital.

G. B. RHODES.

L'ASPERGILOSE PULMONAIRE PRIMITIVE. M. MACAIGNE and P. NICAUD, Presse méd. **34**:401, 1926.

The pathogenesis of *Aspergillus fumigans* has been the object of numerous investigations by Chantemesse, Widal, Bodin, Macé, Gaucher, Sergent and others. Dieulafoy, however, considered that pulmonary aspergillosis is extremely rare as a primary affection of the lungs, and that being secondary in these organs it develops frequently on top of another lesion already existing here, particularly that of tuberculosis. Macaigne and Nicaud's report concerns a woman, aged 70, who died following repeated hemoptysis, and in whom *Aspergillus fumigans* was found at careful postmortem examination to be the single pathogenic agent.

The authors have investigated: (1) the anatomic lesion produced by the parasite, (2) the parasite itself and (3) the clinical symptoms and diagnosis.

1. The left lung alone was involved. It showed progressive sclerosis and extensive thrombosing arteritis. The organ was small and atelectatic, showing cirrhosis more marked at the base, where the pleura was adherent, being 0.5 cm. in thickness. Numerous cavities were found in one fibrotic area, which were lined by smooth walls here and there covered with calcified plaques. Scattered in the fibrotic lung were found loose areolar-like areas which harbored the parasite. The vessels of middle caliber were obstructed by blood clots, and the lumen of the smaller was entirely obliterated by fibrosis. The parasite was disclosed in the wall of the vein and the intravenous clots. Not infrequently it was seen around the arteries, and also beneath the arterial wall. The one lobe in which no parasite could be found showed no demonstrable changes in the arteries.

2. The parasite is stained in sections with difficulty. The best results are obtained by the use of Meisson's triple coloration (hematein, eosine, saffron). Morphologically, the aspergillus represents a baton of varying sizes, being usually from 10-15 mikrons in length, and from 2″ to 3″ in width. It is gathered in sheaflike clusters, which occasionally reach large dimensions. These mycelic forms are disseminated in the parenchyma in a great number, lying freely in the alveolar cavity or lining its wall. Typical forms of reproduction can be seen abundantly in the involved areas. The parasite possesses a necrotizing action. The vascular thrombosis, as well as the necrosis, is due to a toxin emanating from the mycelium. It is possible that analogous to the tubercle bacillus the toxin of the aspergillus leads to scar formation as well as to necrosis. It is remarkable that no leukocytic reaction was present at the level of the lesion. The formation of a "tubercle" by the parasites described in experimental aspergillosis (Dieulafoy, Chantemesse and Widal in the pigeon, Buchard in the parrot, and Hayem in the duck) could not be found by the authors in this case. They consequently consider that the terminology "pseudotuberculosis" applied to aspergillosis of the lungs is justified from the clinical point of view, since it imitates tuberculosis clinically, although incorrect pathologically.

The disease may progress for a number of years. In the case described by Macaigne and Nicaud, the first symptoms appeared at about the age of 18 to 20, when the patient had for the first time a hemoptysis. Similar hemoptysis occurred every two or three months, lasting two or three days. After menopause, she expectorated blood more frequently, this usually being preceded by a marked dyspnea and cyanosis of the face. The general condition of the patient was not affected by the pulmonary lesion.

B. M. Fried.

Experimental Study of Avian Tuberculosis. C. Hruska, Boll. d. Ist. sieroterapico, Milan **5**:109, 1926.

In guinea-pigs infected with the avian tubercle bacillus, the extent of the lesions and the sensitivity to avian tuberculin depended on the toxicity of the culture. Subcutaneous injections of avian tuberculin produced intoxication and death typical of avian tuberculosis. This procedure is suggested for the titration of avian tuberculin. The same results were not obtained in guinea-pigs infected with human or bovine strains.

Ethel B. Perry.

STUDIES ON THE PRIMARY TUBERCULOUS COMPLEX AND ON REINFECTION. H. LIEGEN, Beitr. z. klin. u. Tuberk. **63**:143, 1926.

Studies on serial sections of tuberculous primary foci lead to the conclusion that it is not always possible to differentiate a primary focus from a focus of reinfection. Strong evidence is presented for the possibility of an endogenous reinfection, starting from the primary focus and spreading along the primarily infected lymph channels.

MAX PINNER.

VITAL PHENOMENA OF CORYNEBACTERIA. L. BITTER, M. GUNDEL and T. GARCIA SANCHO, Centralbl. f. Bakteriol. O., I **97**:132, 1926.

Diphtheria bacilli in general produce more acid from glucose than pseudo-diphtheria bacilli, but certain avirulent strains occur that have a greater tendency to acid production. Again, diphtheria bacilli may also produce more alkali than the pseudo forms, but pseudo forms may be encountered that produce more alkali. Diphtheria bacilli reach their acid maximum in shorter time, while the pseudo forms reach their alkali maximum in the shorter period. On this basis a differentiation is possible. It was possible experimentally to change a pathogenic form to an apathogenic form in forty-eight hours and also to reverse the process. This may occur in nature.

E. E. ECKER.

EXPERIMENTAL SCARLET FEVER. S. J. ZLATOGOROFF, W. S. DERKATSCH and S. J. NASLEDYSCHEWA, Centralbl. f. Bakteriol. O., I **97**:152, 1926.

Rabbits and monkeys (*Macacus rhesus*) do not show in experimental scarlet fever the same picture as occurs in man. Experimental scarlet fever is a disease "sui generis." Experimental scarlet fever in animals can be produced with materials containing streptococci (blood, organs, etc.) or with materials free from the organisms. The substance producing the disease passes through a filter, and is found in the mouth, blood and organs of the patients. A "passage virus" can be obtained from animals. It activates the streptococcus and confers on the organisms antigenic qualities.

E. E. ECKER.

VACCINATION ENCEPHALITIS AND POLIOMYELITIS. F. LUCKSCH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:203, 1926.

The reports from various places in Europe of encephalitis following vaccination for smallpox has interested a number of investigators. Lucksch has two other articles (*Med. Klin.* **20**:1170, 1924, and **21**:1377, 1925) in which he deals with the investigations and animal experiments he made as a result of post-mortem examination of the bodies of a few children dying from this form of encephalitis. From Holland, Bastiaanse has reported thirty-five cases, and other reports have come from Switzerland, Austria, Denmark and Germany. In this last article by Lucksch, he attempts to summarize developments in a general way.

The changes encountered in the brain and cord resemble closely those accompanying epidemic poliomyelitis and epidemic encephalitis, a nonsuppurative inflammation characterized by an exudate of cells principally about the blood vessels, mainly in gray matter and especially in the substantia nigra of the pons. However, more involvement of the white substance in this post-vaccination encephalitis and a greater participation by neuroglia in formation of the cellular exudate have been noted.

The interval between vaccination and appearance of symptoms apparently is without relation to the clinical variety the disease eventually assumes, for

the first symptoms occur regularly at or about ten days after vaccination. The symptoms are such that there is a close simulation of tetanus, of poliomyelitis or of epidemic encephalitis with or without paralysis of the eye muscles, or the symptoms may be limited to those indicating meningeal irritation, "meningitis serosa." No alterations occur in the progress of changes at the site of vaccination, the evolution of the vesicles to pustules and to healing, to indicate that encephalitis may subsequently develop. The seasonal prevalence of this form of encephalitis is quite like that of the epidemic variety, but it has been observed where and when the epidemic form has been entirely absent. The mortality is high when vaccination encephalitis resembles epidemic encephalitiis. The cerebrospinal fluid remains unchanged and the brain is grossly unaltered, except with the so-called serous meningitis.

Lucksch urges experimental vaccination of the cornea in rabbits with the spinal fluid (Paul's test) to obtain, if possible, a corneal lesion which may be regarded as characteristic for smallpox virus. As yet but little of value has come from such efforts. He believes that there is at present, a widespread susceptibility of the central nervous system to become diseased, and in addition to the diseases mentioned, he cites the apparently new development in connection with vaccination for rabies, a transverse myelitis, which is, however, extremely uncommon compared with the number of patients for whom this prophylactic vaccination is used.

The medicolegal importance of this postvaccination encephalitis is considerable, and this applies more especially to the form resembling tetanus. The physician may be accused of improper methods, or the virus employed may be condemned. The possibility that some of the unfortunate sequences of vaccination occurring a number of years ago attributed, but not proved to be due, to tetanus, is not discussed by Lucksch.

E. R. LeCount.

Alterations in the Serologic Type of Pneumococcus. E. Berger and B. Engelmann, Klin. Wchnschr. **5**:599, 1926.

Type III pneumococcus, on transition into modification A, acquires the serologic character of the type II organism.

Arthur Locke.

Filarial Infection of Birds. S. S. Wail, P. Popow and F. Prjadko, Virchows Arch. f. path. Anat. **259**:642, 1926.

In crows infected with microfilaria of the species *Diptorienna tricuspis*, the authors describe the localization of the parasites in the capillaries of the brain, this localization being associated with degeneration and neuronophagy of the ganglion cells.

O. T. Schultz.

Pathology of Scarlet Fever. N. Sysak, Virchows Arch. f. path. Anat. **259**:647, 1926.

Sysak summarizes the postmortem pathologic observations in thirty-two cases of scarlatina. A hemolytic streptococcus was obtained from the heart's blood in 90 per cent of the cases. The streptococci showed considerable variation in cultural reactions and in virulence, to which variations the author believes the manifold character of scarlet fever may be ascribed. The changes noted in the internal organs were such as had been described by previous observers.

O. T. Schultz.

DUST-BORNE INFECTION IN TUBERCULOSIS. B. LANGE, Ztschr. f. Hyg. u. Infectionskrankh. **106**:1, 1926.

The author first investigated under what conditions bacteria which had been deposited on various materials with floating droplets would become detached as fine dust. His experiments showed that within a few hours after contamination of rough materials like handkerchiefs and cloth, even moderate handling, and to a greater extent brushing, caused bacteria to be detached and to remain suspended in the air with the dust for a considerable time. Similar experiments with the smooth surface of a linoleum floor were not so successful. Next he determined the length of survival of tubercle bacilli in sputum dried in a thin layer in daylight. He found that there is no noticeable decrease in the number of living tubercle bacilli within the first hours. A marked diminution did not occur until the second day, and even then it was not considerable. He did not obtain evidence of a decrease in virulence of the bacilli in the dried sputum. Finally, he exposed guinea-pigs to the dust arising from objects which had been contaminated with sputum or droplets containing tubercle bacilli. The pieces of cloth used were beaten or brushed in closed cages containing guinea-pigs. Of thirty-six guinea-pigs used, nine, or 25 per cent, contracted a typical pulmonary infection. Lange concludes that among all other methods of transmission of human tuberculosis dust infection is the most important one.

STREPTOTHRIX INFECTION. MANDELSTAM, MORITZ and KALININ, A-lexis (Leningrad) Ztschr. f. klin. Med. **103**:305, 1926.

The case of a man, aged 53, with a history of a syphilitic chancre thirty years ago, is reported. Five months before admission to the hospital the patient showed abscesses at first in the left gluteal region, and later in the right foot, which did not heal after incision. Three or four months afterward he developed intermittent fevers, pyelonephritis, loss of weight and anemia. Blood cultures were sterile. The blood Wassermann reaction was repeatedly negative. A treatment by iodide and mercury gave no improvement. Subsequently the patient developed pain in lumbar and inguinal regions. A puncture in the lumbar region yielded a thick, homogeneous pus in which numerous streptothrix filaments were found. Inoculated into artificial mediums they grew aerobically at 37 C. on glycerin agar and glucose agar. Inoculated into animals the streptothrix proved pathogenic to guinea-pigs only. The animals responded to an intraperitoneal infection by loss of weight and by enlargement of the suprarenals only. The blood cultures from these animals showed a pure streptothrix. The authors quote Plaut tothe effect that in cases of chronic suppuration whether of the viscera or external organs the possibility of a streptothrix infection should be considered always.

B. M. FRIED.

CONTRIBUTION ON THE MICROSCOPIC CHANGES IN PELLAGRA. N. D. WINKELMAN, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:38, 1926.

The microscopic changes of pellagra have been the object of numerous investigations. The results obtained can be briefly summarized as follows: 1. Pellagra does not lead to any noticeable microscopic changes. 2. Lesions pathognomonic of pellegra are present not only in the spinal cord but also elsewhere in the body. 3. Pellagra signifies a premature senile degeneration of the entire body. 4. Lesions in pellagra are essentially a generalized hyaline degeneration of the blood vessels.

Winkelman has investigated the central nervous system of four clinically typical cases of pellagra. In all four cases he found a characteristic triad: (1) vascular degeneration approaching closely hyaline degeneration, confined almost exclusively to the small vessels of the pia and nervous parenchyma; (2) a diffuse fatty degeneration involving ganglion cells, glia cells and the vascular coats (mesoderm and ectoderm); (3) changes in the ganglion cells in the motor area of the cortex and subcortex in the sense of Nissl's "primary irritation."

All these lesions are independent of one another, and are the direct result of the disease. The lesions are mainly localized in the centralis anterior, and in the anterior and posterior horns of the spinal cord. The fatty degeneration is most marked in the forebrain and to some degree in laminae III and V. In one case there was present a degeneration of the posterior column accompanied by focal degenerative changes in the posterior root. On the whole, the lesions found are degenerative and not inflammatory in character.

The author's opinion is that in the present state of our knowledge pellagra cannot yet be considered a systemic disease.

B. M. Fried.

Studies on Food Poisoning Especially of Aërtrycke Bacilli. Kikuo Sakai, Tohoku J. Exper. Med. **7**:307, 1926.

From a cultural and serologic study of bacteria of the paratyphoid-enteritidis group the conclusions were that most cases of food poisoning were caused, not by the Schotmüller bacillus, but by other paratyphoid organisms, such as the mouse typhoid and hog cholera bacilli, and that typhoid conditions could be produced by many of the paratyphoid bacilli, especially by paratyphosus B (Schotmüller), but that both the typhoid and the gastro-enteritis conditions could result from the same organism.

Immunology

Experiments on the Sensitivity of the Human Skin to the Toxin of the Bacillus of Shiga-Kruse. H. Brokman and F. Przesmycki, J. Immunol. **11**:361, 1926.

Experiments are presented showing that the negative skin reaction to the products of the Shiga-Kruse bacillus in human beings depends on the presence of antitoxin in the blood. The antitoxin is specific and, as in the case of "natural" immunity to diphtheria, it appears spontaneously in the individual, without a previous attack of the disease or artificial immunization. If this presence of dysenteric antitoxin in human beings provides an actual immunity against infection with dysentery, then the way must be open to attempt an active immunity in the same way as is done in respect to diphtheria and scarlet fever. We have actually begun to make this attempt with dysentery anatoxin. These experiments will be the subject of our next communication.

Authors' Summary.

The Effect of Heat and Hydrogen Ion Concentrations on the Extract of Short Ragweed. Leslie N. Gay, J. Immunol. **11**:371, 1926.

An extract of short ragweed pollen was subjected to heat — 100 C. for periods of time ranging from one to twenty minutes. The extract was heated in concentrated solution and then diluted; it was also diluted and then heated. These dilutions were then titrated intradermally in patients suffering from

ragweed hay-fever, and the reactions were studied by comparison. Variation of the reactions in a person suffering from a mild case of hay-fever and in one suffering from a severe case was observed.

An extract of short ragweed pollen was subjected to varying degrees of heat: 60 C., one hour; 100 C., one hour; and autoclaved at 15 pounds' pressure, twenty minutes. This extract was diluted: one part to 1,000, one part to 10,000 and one part to 100,000; the intradermal reactions were studied and compared.

An adjustment of the neutral ragweed extracts to p_H 8.4 and 4 was made; these solutions were diluted, heated as described above and then titrated in ten patients.

AUTHOR'S SUMMARY.

AN IMMUNOLOGICAL STUDY OF AN ATYPICAL MENINGOCOCCUS STRAIN. MARY B. KIRKBRIDE and ALICE I. HUTTON, J. Immunol. **11**:393, 1926.

This strain is a striking example of a meningococcus giving rise to a serious infection that apparently yielded to treatment with polyvalent serum in which, when first isolated and for some time afterward, it failed to agglutinate.

THE EFFECT OF SUPRARENALECTOMY ON ACTIVE ANAPHYLACTIC SHOCK IN THE WHITE RAT. R. H. FLASHMAN, J. Infect. Dis. **38**:461, 1926.

Of a group of four white rats sensitized from nine to fourteen days after bilateral suprarenalectomy and given intraperitoneal injections of horse serum eleven days later, two died and two had moderate symptoms. Of a group of five rats sensitized from nine to eleven days before suprarenalectomy and given injections from two to six days after the operation, four died and one had moderate symptoms. Of a group of six control rats similarly sensitized and given a later dose, three had no symptoms and three had slight symptoms. These results indicate that bilaterally suprarenalectomized rats show a markedly increased susceptibility to anaphylactic shock, produced by intraperitoneal injections of horse serum. This effect is obtained whether the animals are sensitized before or after suprarenalectomy, and seems related chiefly to the degree of suprarenal insufficiency.

AUTHOR'S SUMMARY.

THE AMOUNT OF ANTITOXIN TO STREPTOCOCCUS SCARLATINAE PRESENT IN THE BLOOD OF CONVALESCENT SCARLET FEVER CASES. HERBERT HENRY and F. C. LEWIS, Lancet **1**:709, 1926.

If the unit of antitoxin be taken as that amount which gives complete neutralization of one skin test dose, then of twenty children with scarlet fever seventeen were found to yield a serum which contained 50 units or more of antitoxin, whereas of the children who did not have scarlet fever, only eight reached this titer. Of the twenty children who had scarlet fever, nine yielded a serum containing 125 units or more, whereas only three of the children who did not have the disease did so. The 250 unit level was reached by five children who had scarlet fever and by one child who did not have it.

The blood groupings of these children were determined for a purpose other than that with which the present report concerns itself. It is of some interest, however, to note that although the distribution of the groups taken throughout the whole collection of serums approximates the normal, yet there would seem to be a preponderance of children from group II among those convalescing from scarlet fever and of group I among those who did not have scarlet fever.

AUTHORS' SUMMARY.

THE DICK TEST IN MEASLES. JEAN PARAF, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:506, 1926.

Uncomplicated measles had no effect on the Dick test. The reaction was the same in all cases during and after the attack. Twenty-three children with complications following measles had positive reactions at the beginning of the illness and negative reactions afterward. In seventeen of these children streptococci were found. Three of them had positive tests before they developed the measles. The author concludes that measles complicated by streptococcus infections can cause a positive Dick reaction to become negative, and that doubt of the specificity of the Dick test for scarlet fever is justified.

B. R. LOVETT.

INTENSITY AND TIME OF STIMULATION IN THE ANTITOXIN IMMUNITY OF SMALL ANIMALS. GIULIO PUPILLI and MARCO PUPILLI, Boll. d. Ist. sieroterap. Milan **5**:114, 1926.

The immunization of guinea-pigs and white rats against diphtheria and tetanus toxin can better be accomplished by injections, at four, five or seven day intervals, of slowly increasing doses than by daily injections of small doses that tend to produce what Zironi called "paradoxical sensitivity."

STUDIES ON THE ACTION OF METALLIC COLLOIDS ON IMMUNIZATION. GENESIO PACHECO, Mem. do Inst. Oswaldo Cruz **18**:119, 1925.

Metallic colloids intervene favorably by increasing the agglutinins in circulation when the latter are present and of specific nature. On the temperature and development of the infection their action is nonexistent; in reconvalescents they may provoke the reappearance of fever (recidive?); they raise the temperature when there is fever; when there is none, there is a rise of temperature not amounting to one degree and rarely exceeding normal. As in regard to these reactions, all of the colloids acted in the same way.

The increase in agglutinins observed must have been caused by the colloids, since in the control case the agglutination power was unaltered.

AUTHOR'S SUMMARY.

IMMUNIZATION AGAINST DIPHTHERIA WITH ANATOXIN. P. S. SRODOWSKI and H. BRENN, Centralbl. f. Bakteriol. O., I. **97**:125, 1926.

The authors confirm Ramon's work. The change of toxin to anatoxin is gradual, depending on the concentration of formol and the time. Not every toxin is readily converted to anatoxin. A complete and constant change occurs in thirty days with 0.5 per cent formol (40 per cent) and a temperature of from 40 to 42 C. Guinea-pigs resist 2,000 to 6,000 minimal lethal dose. The flocculation capacity remains. Addition of 0.5 per cent phenol destroys the flocculation capacity of the product. A good flocculating anatoxin has a high antigenic power. Immunity is established in from fourteen to forty-five days, rarely in from fifty to fifty-two days. Phenol lessens this power. A mixture of anatoxin and antitoxin results in reduction of antigenic value. They vaccinated 200 children and adults. Young children resist vaccination better and withstand larger doses. They give to young children from 0.3 to 0.5 cc. and even from 0.5 to 1 cc. and to school children from 0.2 to 0.3 cc. They believe that the French workers inject too much (from 0.5 to 1 cc.). As

small a dose as 0.1 cc. may produce a negative Schick reaction. Guinea-pigs that received the anatoxin but in which immunity was not as yet established became extremely sensitive to the toxin. The same occurs in man during this period. It is probably an allergic manifestation. Anatoxin is a more effective immunizing agent than the hyponeutral toxin-antitoxin mixture.

E. E. Ecker.

Mutation Forms of Dysentery Bacilli Shiga-Kruse. M. Jsabolinsky and W. Gitowitsch, Centralbl. f. Bakteriol., O., I **97**:148, 1926.

Variations occur. These variations may be closer to the typhoid bacilli or to the colon bacilli. It is a question of adaptation. Some of the variants lost their agglutinating character in a high dilution of the specific serum.

E. E. Ecker.

Complement-Fixation in Rhinoscleroma. Gerhard Quast, Centralbl. f. Bakteriol., O., I **97**:174, 1926.

Biologic differences exist between rhinoscleroma bacilli and other encapsulated bacilli. By means of complement fixation a differentiation is possible. Complement-fixing bodies occur in this disease in demonstrable amounts.

E. E. Ecker.

Formation of Bacteriolysin in Experimental Cultures of the Spleen. F. Schilf, Centralbl. f. Bakteriol. O., I **97**:219, 1926.

A vibriolysin was demonstrated in growing cultures of the spleen of the rabbit and of the guinea-pig inoculated with a small amount of the killed organism.

E. E. Ecker.

The Pathogenesis of Bronchial Asthma, Especially in Its Relation to Anaphylaxis. K. Eskuchen, Klin. Wchnschr. **5**:686, 1926.

This is a general review of the hypotheses which have been presented in regard to the pathogenesis of bronchial asthma. Hypersensitivity to an allergen, while principally of an anaphylactogenic character, may be attributable partly to inherited and constitutional predispositions. The onset of an attack of asthma may be conditioned by a shifting of the vagus-sympathetic balance, occasioning an abnormal sensitivity. The calcium therapy of asthma is based on the capacity of this ion to increase the irritability of the sympathetic [as contrasted to the vagotonic action of the Na^+ and K^+ ions]. The asthmogenic substance need not necessarily be of a protein character.

Arthur Locke.

Experiments with Peroral and Percutaneous Immunization. H. Reiter and A. Kurohawa, Klin. Wchnschr. **5**:744, 1926.

Immunity may be obtained against mouse typhus and staphylococcus infection in mice, paratyphus in guinea-pigs and streptococcus in both mice and guinea-pigs by peroral and percutaneous administration of killed and living cultures and culture filtrates. The incorporation of sodium benzoate into the inoculum increases its effectiveness.

Arthur Locke.

THE COMBINATION THERAPY (SEROLOGIC AND CHEMICAL) OF TYPHUS ABDOMINALIS. HILGERMAN, München. med. Wchnschr. **73**:520, 1926.

Sodium salicylate is a specific chemotherapeutic agent for infections of the typhus bacillus. It may be advantageously employed to increase the effectiveness of typhus antitoxin.

ARTHUR LOCKE.

THE PATHOGENESIS AND THERAPY OF BRONCHIAL ASTHMA. W. STORM VAN LEEUWEN, München. med. Wchnschr. **73**:599, 1926.

Asthmogenic allergens, arising from the decomposition of organic matter by mites and molds, are present in house dust and in the atmosphere of many localities. Relief from bronchial asthma may be obtained by rest in allergen-free rooms. These rooms should, if possible, be air-tight and constructed and furnished with materials, such as glass, asbestos and steel, which do not favor the growth of parasites. The mattresses should be sterilized regularly and the ventilation either with air carried in from some distance above the building, or with air which has been freed from its colloidal suspension of water and adsorbed organic matter by undercooling and condensation.

ARTHUR LOCKE.

THE RELATION OF PRECIPITINOGENS TO TOXINS OF TOXIC CHOLERA VIBRIOS AND THEIR PARTICIPATION IN FLOCCULATION BY SPECIFIC SERUMS. M. EISLER and N. KOVACS, Wien. klin. Wchnschr. **39**:469, 1926.

In the course of specific precipitin reactions with filtrates of broth cultures of a cholera vibrio, there was loss of toxin due to adsorption of toxin by the precipitate. The toxin was shown to be independent of the precipitinogens. This toxin did not cause flocculation with its antitoxin.

FRACTIONATION OF HEMOLYTIC AMBOCEPTOR SERUM. K. LAUBENHEIMER and HILDEGARD VOLLMAR, Ztschr. f. Hyg. u. Infektionskrankh. **106**:202, 1926.

By means of electric ultrafiltration, the euglobulin fraction can be separated accurately from the serum. The hemolysins are contained only in this fraction, a result that is different from that obtained by Ruppel with electro-osmosis. The paraglobulin fraction and the albumin were found to be free from hemolysins. The amboceptor removed with the euglobulin possesses the same hemolytic action as the serum from which it is obtained. The titer of the amboceptor removed with the euglobulin diminishes with time after dissolving the euglobulin. By dissolving the amboceptor euglobulin in hemolytic immune serum, the titer of the serum can be increased greatly.

DOES ANTIBODY FORMATION RESULT AS A REFLEX OR FROM THE RESORPTION OF ANTIGEN? HANS COHN, Ztschr. f. Hyg. u. Infektionskrankh. **106**:209, 1926.

Intramuscular injections of 0.2 cc. of horse serum were made into the incompletely amputated leg attached only by isolated skin, muscle, bone, sciatic nerve, femoral artery or vein. Two minutes after the injection the connection was cut and the wound repaired, and four weeks later each guinea-pig was tested for sensitization by an intravenous injection of 0.1 cc. of horse serum. Only when the distal stump was connected by the vein, or when, as in certain control animals, connections such as nerve or muscle were accompanied by conditions for good circulation — in other words, only when resorption of the

antigen by the circulatory system was possible — were the guinea-pigs found sensitized. With the femoral vein connection sensitization occurred within one-half minute, but not within three seconds. There was no evidence that antibody production could be effected by tissue conduction of a "stimulus."

ETHEL B. PERRY.

EXPERIMENTAL STUDIES OF PRECIPITINS AND THE SPECIFIC CUTI-REACTION. 1. APPEARANCE AND DISAPPEARANCE OF PRECIPITIN IN RABBIT SERUM. GICHU SHOJI, Acta dermat. **7**:329, 1926.

Precipitins for human, sheep and horse serums and egg white in the blood of rabbits varied little in time of appearance and duration with different modes of injection, intradermal, subcutaneous, intraperitoneal, intravenous and intramuscular; but, for egg white the precipitin appearance was later than for the other antigens, the maximum higher and the persistence more brief, while for the human serum the response was least and persisted longest, even for one year. Injections of small amounts (0.1 cc.) every five or seven days were as effective as 1 cc. amounts. Precipitins appeared usually after the second or third injection, and the maximum reached after the third or fourth was little changed by more injections.

ETHEL B. PERRY.

THE SPECIFICITY OF THE URINARY INTRACUTANEOUS REACTION IN TUBERCULOUS PERSONS. C. C. VVEDENSKY, Arch. d. sc. biol. **25**:293, 1926.

The author studied the blood serum of tuberculous men and animals by means of the complement-fixation reaction, using as antigens extracts of tubercle bacilli, emulsions of bacilli, and the sterilized and evaporated urine of tuberculous persons in whom auto-injection of the urine produced a local reaction. Seventy serums were studied, from normal and tuberculous men and animals. With the serum of tuberculous subjects, the Bordet-Gengou reaction gave positive results (strong inhibition of hemolysis); with the serum of healthy subjects the reaction was negative. The urine differed only quantitatively from the bacillary antigens. The following conclusions were reached: Sterilized and evaporated urine of a tuberculous subject which gives a local reaction on autoinjection, contains specific tuberculous substances which can be discovered by the Bordet-Gengou reaction. The specificity of the auto-urinary reaction is confirmed by the complement-fixation reaction. The quantity of specific tuberculous substance in the urine varies at different times. For the exact appreciation of results of the complement-fixation reaction, it is necessary to titrate all ingredients with normal serum and to control them all.

B. R. LOVETT.

Tumors

THE REPEATED INOCULATIONS OF ANIMALS WITH SO-CALLED "CANCER ORGANISMS." S. L. WARREN and H. E. PEARSE, Am. J. M. Sc. **171**:820, 1926.

Two hundred and forty-one mice of a strain susceptible to mouse cancer inoculations, but in which spontaneous tumors were rare, at weekly intervals were given intracutaneous injections of either the micrococcus of Nuzum or diphtheroids and micrococci obtained from human cancers of the breast. The inoculations were continued until death, or for four months, at which time only fifty mice remained alive, the others having died, usually from septicemia.

These fifty mice were observed for two months more, or for a total of six months. Ulcerations of the skin which readily healed occurred with great regularity. None of the animals showed any evidence of a neoplastic growth except one which developed a spontaneous tumor of the liver. Four rabbits receiving weekly injections of both diphtheroids and micrococci for from three to five months, showed no signs of malignant disease even at the end of six months. No evidence was found that any of these organisms play a primary rôle in the etiology of cancer, though an indirect rôle is possible.

AUTHORS' SUMMARY.

DIAGNOSIS OF PULMONARY NEOPLASM. M. FISHBERG, Arch. Int. Med. **37**:745, 1926.

The author gives a comprehensive discussion on pulmonary neoplasm. Necropsy was performed in thirty-six cases. In thirty-five there were carcinomas and in only one a spindle cell sarcoma. Macroscopically the location of the tumor is: (1) the vicinity of the hilum infiltrating the parenchyma more peripherally, usually of the hilum of the upper lobe; (2) a coarsely nodular mass embedded in the parenchyma of any part of the lung; (3) rarely the diffuse carcinomatous infiltration of one or more lobes, which may resemble an extensive caseous pneumonia, and (4) in three cases "endothelioma of the pleura." Fishberg discusses three clinical forms of the disease: (*a*) pulmonary, simulating tuberculosis; (*b*) pleural, simulating pleurisy, dry or with serous, sanguineous or purulent effusions, and (*c*) excavating, simulating abscess and gangrene of the lung.

S. A. LEVINSON.

THE HYPERSENSITIVENESS FOLLOWING INJECTIONS OF PLACENTAL EXTRACTS. G. H. SMITH and L. K. MUSSELMAN, J. Immunol. **12**:7, 1926.

From the author's experiments the following conclusions are made:

Animals passively sensitized by the intraperitoneal injection of 2 cc. of the antiserum presented severe anaphylactic shock, and in one case died, when female human serum was injected forty-eight hours after the sensitizing treatment. Male serum administered under comparable conditions elicited no reaction. Guinea-pigs actively sensitized with extracts of human placenta present a marked hypersensitivity to human serums. Such animals manifest acute anaphylactic shock on the subsequent intravenous injection of either male or female human serums and a definite reaction to the reinjection of placental extract. This would indicate that the amount of serum present in the placental extract is small, although ample to induce a serum sensitivity. Guinea-pigs sensitized with placental extracts may be desensitized to human serum, or at least to male human serum by intraperitoneal injections of male human serum. Such desensitized animals may still be acutely intoxicated by female human serum in doses which are inactive if administered to normal guinea-pigs. Comparable quantities of male human serums fail to induce acute fatal shock, or if shock occurs it is much less intense than that caused by female serum. Guinea-pigs which have reacted to male human serum with acute but not fatal shock may die of acute anaphylactic shock if given subsequent reinjections intravenously with female human serum. Guinea-pigs passively sensitized with the serums of rabbits which have received a series of injections of placental extract are hypersensitive to female human serum while sensitivity to male human serum is lacking. These differences in the intoxicating effects of male

and female human serums appear to be determined by qualitative factors, suggesting a common antigenic relationship between some fraction of the material of the placental extract and female human serum.

S. A. LEVINSON.

THE INFLUENCE OF ANAPHYLACTIC SHOCK ON FLUID IN THE PERITONEAL CAVITY: II. INFLUENCE UPON THE ORGANIC AND INORGANIC CONSTITUENTS. M. S. FLEISHER, L. L. MAYER and C. M. WILHELM, J. Immunol. **12**:19, 1926.

The authors offer no explanation regarding the difference in the chlorine ion concentration in shocked compared to normal animals. It appears that the difference in osmotic pressure of the recovered peritoneal fluid of shocked and normal animals is due to a higher chlorine ion concentration in the former. Protein constituents in the two kinds of fluids are apparently not different and cannot therefore be factors in the difference in osmotic pressure. Phosphates are also probably not responsible for the difference, although they may play some part.

S. A. LEVINSON.

MELANOMA (SARCOMA) OF THE EYE IN A SYPHILITIC RABBIT. WADE H. BROWN and LOUISE PEARCE, J. Exper. Med. **43**:807, 1926.

A melanotic tumor developed in a defective eye of a syphilitic rabbit following repeated genital inoculations with *Spirochaeta pallida*. The appearance of the tumor coincided with the development of a syphilitic lesion in the same eye, suggesting a relation between the occurrence of the two lesions.

AUTHORS' SUMMARY.

TUMORS OF THE PHARYNGO-HYPOPHYSIAL TRACT. LUCIEN CORNIL, Ann. d'anat. path. et d'anat. normale méd. chir. **3**:237, 1926.

The present report is a summary of a case previously published by Cornil and also of a new case observed by him recently.

Tumors of the "pharyngo-hypophysial tract" are classified by Cornil in three varieties: (1) cysts of Rathke's pouch, frequently seen in children, due occasionally to a hypersecretion of the salivary acini of the wall of the cyst; (2) pharyngo-hypophysial epitheliomas developed at the expense of the remnants of Rathke's pouch — these new growths take an aspect of a cylinder cell or a malpighian epithelioma, the latter showing occasionally the presence of keratin; in a number of cases they have the structure of an adamantinoma characterized by elongated cells which line the surface of the papillae; (3) teratomas.

The first case of Cornil concerned a spinocellular malpighian epithelioma found at necropsy in an insane patient who six months before death showed symptoms of increased intracranial pressure, with blindness, somnolence, headaches, asthenia and cachexia. The second case was found in a man, aged 30. The tumor had a papillary structure lined by an epithelium of the adamantinoma type. The vascular connective tissue axis of the papillae had in places a myxomatous aspect. Of particular interest in this case was the presence in the papillary axis of a peculiar collagen formation made up of agglomerated fibrils disclosed with the stains of Mallory, Masson and Leroux.

B. M. FRIED.

THE TRANSFORMATION OF NORMAL CELLS INTO MALIGNANT CELLS IN VITRO. ALBERT FISHER, Compt. rend. Soc. de biol. **94**:1217, 1926.

Carrel was able to transform embryonic cells into malignant cells by inoculating the former cells mixed with small quantities of tar, arsenic acid or indol. Fisher by doing independently analogous experiments arrived at similar conclusions.

As a material he used splenic tissue from a chick embryo 17 days old, to which tar or the anhydrate of arsenic acid (in a certain concentration) was added. After from seven to ten passages with arsenic acid the cultures were isolated and cultivated for one month in an ordinary fashion, in an equal mixture of plasma and the juice of embryonic tissue. After from four to six passages the coagulated plasma became liquefied, a phenomenon observed also in the cultures of Rous' and other malignant tumors. After nineteen passages in vitro (the last eight without arsenic) two cultures were inoculated into a chicken. Three weeks after inoculation a new growth, about 2 cm. in diameter, appeared at the point of inoculation. A biopsy showed the tumor to be composed mostly of round cells with a tendency to a myxomatous degeneration. The removed tumor inoculated into a new chicken rapidly produced a new growth. Ebryonic tissue mixed with tar gave analogous results.

B. M. FRIED.

CHOLESTERIN IN RELATION TO AGE AND DEVELOPMENT OF CANCER. A. H. ROFFO, Bol. d. Inst. de med. exper. **3**:195, 1926.

The observations of hypercholesterinemia occurring in persons over 40 years of age, with its height at the fifty-fifth to sixtieth year, are summarized with other known factors to support the hypothesis that hypercholesterinemia predisposes to carcinomatous development. Transplantable tumors develop best when 5 months old, a period which coincides with the most pronounced cholesterinemia; during pregnancy when there is a suggested parallelism between the increase of cholesterin and that of the tendency to malignancy, and in precancerous lesions of the skin in which the cholesterin content is about three times that of normal skin.

ETHEL B. PERRY.

GLANDULAR CARCINOMA OF THE THYMUS. HELENE SCHUSTER, Beitr. z. path. Anat. u. z. allg. Pathol. **75**:403, 1926.

In a man, aged 47, the anterior mediastinum was occupied by a large tumor mass, and there were multiple metastases in the pleurae and in the liver. Microscopically the tumor was composed of glandlike alveoli lined by cuboidal and cylindric epithelium, the alveoli being filled with a gelatinous material. No thymic tissue was recognizable as such, and no Hassall's bodies could be found. Although a mucus-secreting glandular carcinoma has not previously been described as originating from the thymus, the author concludes that the tumor described by her arose from this organ, either from the cystlike epithelial lined spaces, which are found fairly frequently in the thymus and are remnants supposedly of the original entodermal anlage, or from misplaced entodermal cells.

O. T. SCHULTZ.

THE METABOLISM OF TUMORS. O. WARBURG, F. WIND and E. NEGELEIN, Klin. Wchnschr. **5**:829, 1926.

Tumor cells may be destroyed by shutting off their supply of available energy. This energy comes from two sources, oxygen and glucose. Destruction of tumor cells may be accomplished in a living animal by decreasing the supply of glucose, whereupon the oxygen supply which is sufficient to maintain the existence of the normal organ is not sufficient to maintain the energy requirements of the tumor cell. Fortunately, the nutrition of tumor tissue is naturally poor. Normal nutrition is at its best in the region of the jugular vein and at its poorest in the region of the portal vein. The nutrition of tumor tissue is three times poorer than that of the portal region. Therefore, if the respiration of the tumor may be successfully limited, it should be destroyed. Rats with tumors were kept in a gas mixture containing 5 per cent by volume of oxygen and a small quantity of ammonia (to lessen acidosis). The oxygen-saturation of the hemoglobin by these mixtures was so reduced that relatively only half of the tumor was supplied with oxygen. The animals were killed after 40 hours' treatment, the tumors were removed, and the metabolism of a portion was measured in vitro. The greater part of the tumor cells was dead. Only a thin external band retained its normal metabolism.

ARTHUR LOCKE.

Medicolegal Pathology

THE BEARING OF RECENT NEUROLOGIC STUDIES ON SUDDEN UNEXPECTED DEATH. G. ANTON, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:143, 1926.

This sketchy comment is one of several devoted to the commemoration of the sixtieth birthday of Carl Ipsen, for many years at the head of the medicolegal department of the University of Innsbruck. It deals with the statics of the posterior cranial fossa and the cerebellum; the part played by the tentorium in making this fossa a cavity separate from that occupied by the cerebrum; the suspension of the cerebellum, midway between the fluid in the larger cranial cavity and that in the spinal canal, and how these and other conditions peculiar to this region may be concerned with sudden death.

From pressure due to tumors, hydrocephalus, etc., the worm and tonsillar lobules of the cerebellum may be driven into the upper end of the spinal canal so that death by pressure on the medulla promptly occurs when the head is bent backward. Surgeons have noted the pulseless state of the cerebellum in bilateral openings below the groove for the transverse sinuses made to relieve pressure and the return of pulsation when fluid has been withdrawn. The need of recumbency to prevent impaction of the cerebellum in the foramen magnum and compression of the medulla following withdrawal of large amounts of cerebrospinal fluid is again emphasized.

Anton also urges the need of study of the atlanto-occipital and atlanto-epistropheal joints by roentgenography and other methods, because alterations in them, such as ankylosis or abnormally great motility, are as intimately concerned in exerting bony resistance below the cerebellum as is the tentorium in furnishing a like resistance above the cerebellum and other structures in the posterior fossa. He cites, among other examples of this relationship, the influence developmental anomalies in these bones and joints possess on passage through the birth canal, and states that examination of them is definitely

indicated in cases of asphyxia at the time of birth. Examination is also advised preceding suboccipital removal of cerebrospinal fluid by tapping the cisterna of the arachnoid at the junction of the medulla and cerebellum.

E. R. Le Count.

Poisoning with Noxious Gases and Its Determination. F. Flury, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:149, 1926.

The intangibility of poisonous gases, the difficulty or impossibility of recovering such poisons from the body and an absence of symptoms peculiar for each gas have led to the association of mystery with the deaths they produce; this is especiailly true of impressions such deaths have on the laity. No phase of practical toxicology possesses difficulties comparable with those encountered in the detection of such gases and in estimating their harm. The absence of any complete textbook or other account of these poisons compels each toxicologist to rely on his own experience and ability.

There are about 1,000 poisonous gases known, including those developed by war. With entrance into the body of most fluid and solid poisons the lethal dose is usually exceeded when death results, but with the poisonous gases the toxicologist works with barely the amount necessary to kill and it may be with less, since through their volatility some pass out of the body after death. Because of their increased importance and variety, so many methods have been devised dependent on the minute amounts available for detection, that an entirely new field has appeared in toxicologic and pharmacologic chemistry.

These "micromethods" have been applied with considerable success to gases of the aromatic series, gases with amino combinations, those containing such metals as lead, mercury, antimony, arsenic and nickel, to nitro and nitroso compounds, carbon monoxide, cyanogen and its derivatives and to the numerous gases containing sulphur. The "microanalysis" of tissues of the respiratory organs to secure substances yielding desired color or precipitation reactions is often referred to now, and also "microdistillations" of the urine for chloroform and closely related poisons. Many of these "micromethods" lead to quantitative estimates.

Some of the gases like hydrogen and nitrogen are indifferent and cause death by replacing oxygen. Others are resorbtive and enter the blood or body tissues. Some provoke a marked local reaction and others possess mixed properties. Many have no lethality constant, and for others the lethal dose, a product of the concentration and duration of inhalation, is definitely known. The absolute quantity inhaled of some gases, such as phosgene, is the chief factor of their poisonous action. Some are odorless and so nonirritant that no warning is obtained of their presence or of the danger at hand. By others the sense of smell may be blunted. Phosgene is a good example of a gas poisonous by its local irritation; others are vapors from acids, gases containing the halogens, nitro compounds, isocyano-derivatives and arsenuretted hydrogen.

Only a few of the many industries in which chemical processes have an important rôle have succeeded in reducing the hazards from poisonous gases to a minimum. New methods concerned with the refinement and manufacture of food products, oils, varnishes, fats, resins, dyes, rubber and other gums are being elaborated constantly, and the various industries in which these methods are utilized are rapidly increasing. Hydrocyanic acid and its derivatives are at present largely employed in combating animal and vegetable pests

for food stored or in transit. Arsenic in a great variety of forms and some of the halogens, notably fluorine compounds, are used extensively as dusts or sprays in agriculture. To destroy parasites pathogenic for plant and animal life and lessen the huge damage of termites, ants and locusts, many new industries have already arisen from the efforts which are being made to utilize the resources of tropical countries and render them habitable.

Poisonings occur among the laborers where these new chemical methods are in operation from accidental breaking or unsuspected perviousness of containers and conduits for these gases, from the evaporation of fluids and from gas explosions; but many poisonings also occur in places where the gases or the substances yielding them find their economic application.

The symptoms produced by many of these poisons are so devoid of characteristics and simulate so closely those due to disease that frequently the first clue to the real nature of the trouble is obtained from knowledge of the patient's habits, environment, occupation, etc. The symptoms caused by other gases are characteristic when the poisoning is acute, but altogether wanting in outstanding peculiarities in chronic poisoning. When the chronic has been altogether without any preliminary acute poisoning, great difficulty attends determination of the cause of the symptoms. The inhalation of some of the noxious vapors in weak concentration is accompanied by so much of neutralization by the body that the amounts necessary to produce death under such conditions are unknown. This applies especially to narcotic gases. It is well known that inhalation of hydrocyanic acid gas in strong concentration causes death with most unusual abruptness. On the other hand, if the cyanogen in the gas is in combination with halogens or the esters of fatty acids, its inhalation may go on for hours and death be due, if it occurs, to damage to the lung tissue.

The lungs are usually mottled red and purple with the intervening tissue paler from emphysema often interstitial, wholly or in part; but the changes in the lungs vary markedly in acute poisonings. The pulmonary edema caused by some gases, it is believed, results from their action on the blood, the blood impoverishment so affecting the heart that the edema of the lungs follows. The edema produced by other gases such as phosgene is apparently a result of changes the gases cause in the lung parenchyma. The lesions in the lung usually heal completely, but chronic bronchitis and asthma may be sequels. Apparently the changes in the lungs are entirely without causal relation to pulmonary tuberculosis developing subsequently.

Necrosis of the mucous membranes of the nose, accessory nasal sinuses, pharynx, larynx and trachea follows inhalation of some of the more irritant heavy gases such as dichlorethyl sulphide ("mustard gas"), and these may be followed by anosmia, aphonia or permanent hoarseness. If the cause of the lesions in any portion of the air passages is not determined early and the first lesions become greatly changed by infection, diagnosis may be especially difficult.

A considerable destruction of liver tissue, like acute yellow atrophy following the inhalation of gases containing arsenic, phosphorus or nitro compounds, has recently excited great interest notwithstanding the fact that similar results due to chloroform have been known for some time. Characteristic odors are given to the urine by substances passed out that way from some of the poisonous gases containing complicated organic compounds of the phenol and benzol groups, and halogens.

A purpura cerebri is encountered in postmortem examinations, sometimes in the bodies of those with motor restlessness, stupor or coma, and sometimes

when there have been no symptoms pointing to alterations in the central nervous system. That the results of chronic poisoning are unknown applies to nearly all the poisonous gases and especially to long continued inhalation in weak concentration. It also applies to the results of inhaling first one and then another poisonous gas and to the inhalation of mixtures.

Flury, who is the director of the Institute for Pharmacology in the University of Würzburg, concludes his interesting account by emphasizing the need in these chemical industries for physicians with special training in hygiene, toxicology and pathologic anatomy.

E. R. Le Count.

Regarding Changes Caused by Maggots in Dead Bodies. G. Hanser, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:179, 1926.

Following the discovery of the body of a young woman partly submerged on the shore of a reedy fish-pond, a sailor, known as her lover and responsible for her pregnancy of a few months' duration at the time of death, was accused of her murder. Maggots had eaten open one side of the thorax, and entirely consumed the lungs, heart and external genitals, and a loop of small bowel projected from the vagina. The tubes, ovaries and all but the cervix of the uterus were absent, and there was a hole in the colon. It became necessary to decide whether these organs were missing from congenital absence or from external violence, or whether they, too, were eaten away by maggots.

The last explanation was the only one found satisfactory, and this conclusion resulted mainly from experiments made with the genital organs from the bodies of ten women, repeating as far as possible the conditions concerned with the body found on the fish-pond shore and implanting in the vagina of such organs the eggs or larvae of a small blue-bottle fly, *Lucilia caesar*.

The vagina was eaten away in all but one; the cervical part of the uterus was destroyed twice, left intact seven times and partly consumed once; the tubes were consumed in eight cases, and all the ovaries except the left, in one instance, were disposed of by the maggots.

The accused was found guilty of murder, however, chiefly from strong circumstantial evidence, and a sentence of sixteen years was imposed.

E. R. LeCount.

Murder or Suicide from Bullet Wounds of the Head. R. Kockel, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:193, 1926.

There are recorded in the literature of legal medicine a number of instances of suicide with conclusions that the deceased fired more than one bullet into or through the head. Goroney reviewed such occurrence in this issue of the *Zeitschrift* (**7**:145).

The question in this instance, reported by Kockel, had associated with it the following circumstances: one bullet path sagittally a little to the left with the left carotid artery severed at its entrance into the cranium and the bullet in the scalp behind; another wound across the head from left to right and the bullet in a felt hat lying under the head; the head lying on the outside of the hat with the bullet hole in the hat from without inward as was evident from scalp hair carried into the path of the bullet in the hat; three of the six cartridges missing from the revolver; one shell found 6 meters away and another 70 cm. from the body; the revolver found in the angle formed by the left shoulder with the neck of the deceased, a woman missing for two months; the body found in the woods

some distance from the hotel where the deceased was stopping with the accused, an unmarried lover who claimed she had committed suicide after leaving him following a quarrel; and conviction of the accused based on the necessity of the transtemporal wound having been a second wound, sustained as the deceased lay on the hat, and the impossibility of its self-infliction after injuries due to the sagittally-directed bullet which passed through the head.

Other circumstances leading the jury to find a verdict of conviction were the distance that sound made by firing the revolver carried, and the bearing that this had on statements of the accused as to his whereabouts when the shots causing death were fired; also efforts made by the accused to dispose of the effects of the woman soon after her disappearance.

About six months after the trial was ended and the accused had begun his term of imprisonment, the missing third shell was found and identified by the hammer and other marks it bore and their correspondence to marks on the other two shells. It was found 1.5 meters from where the head had lain. This led to the conclusions that the shell found 6 meters from the body contained a bullet which was fired at some distance and missed hitting the woman, that the second shot took effect making the front to back wound and causing the woman to fall, and that the last shot was fired into the left temple as she lay with her felt hat crumpled under her head. No new trial resulted from this new evidence.

The bone about the wound of entrance in the left temple was powder-blackened, but the condition of the other wound of entrance was not learned at the first examination. Kockel, therefore, urges that the soft tissues about bullet wounds and those containing bullet paths be removed from the body and preserved for examinations which may help to determine the distance from which bullets are fired.

E. R. LeCount.

Technical

The Early Diagnosis of Pregnancy by Methods of Precision: Further Observations on Sugar Tolerance Tests. Final Report. J. C. Hirst and C. F. Long, Am. J. M. Sc. **171**:846, 1926.

Early diagnosis of pregnancy may be made by the alimentary glycosuria test with a precision of from 92 to 94 per cent.

Arthur Locke.

The Diagnostic Value of Color of the Blood Serum in Pernicious Anemia. A. M. Fishberg, Am. J. M. Sc. **172**:81, 1926.

Observation of the serum color is of value in differential diagnosis between secondary anemia due to carcinoma and pernicious anemia. The blood serum is more highly pigmented during the active periods of pernicious anemia than it is normally.

Arthur Locke.

Diagnostic Value of the Kottmann Reaction in Thyroid Dys-Functions. I. Katayama, Am. J. M. Sc. **172**:84, 1926.

The Kottmann reaction has little diagnostic value in detecting hyperfunction or hypofunction of the thyroid.

Arthur Locke.

BILIARY SYSTEM FUNCTION TESTS. W. P. MURPHY, Arch. Int. Med. **37**:797, 1926.

The author believes that the Rosenthal modification of the phenoltetrachlorphthalein test is not of practical value as a diagnostic aid, except possibly in relation to complications of pregnancy. The icterus index is of definite diagnostic value in distinguishing between the primary and the secondary type of anemia. The normal variation of the index is from 4 to 6. Figures above or below this should be considered abnormal. If obstruction of bile ducts is transient, blood for the test should be obtained within from twelve to twenty-four hours after possible obstruction has occurred. In the absence of anemia, liver damage or duct obstruction, the index should be normal. Stones in the gallbladder should not give an increase of bilirubin in the serum.

S. A. LEVINSON.

STUDIES ON THE OXYGEN-, ACID-, AND BASE-COMBINING PROPERTIES OF BLOOD: II. A RAPID METHOD FOR THE PREPARATION OF CRYSTALLINE ISO-ELECTRIC HEMOGLOBIN BY THE ELECTRODIALYSIS OF RED BLOOD CELLS. W. C. STADIE and E. C. ROSS, J. Biol. Chem. **68**:229, 1926.

A 60 to 70 per cent yield of crystalline, iso-electric hemoglobin may be obtained by the electrodialysis of washed erythrocytes.

ARTHUR LOCKE.

A COMPARISON OF THE FOLIN-WU AND THE NEW BENEDICT METHOD FOR SUGAR IN BLOOD AND CEREBROSPINAL FLUID. J. D. LYTTLE and J. E. HEARN, J. Biol. Chem. **68**:751, 1926.

Simultaneous blood and cerebrospinal fluid determinations were made by the Folin-Wu and the new Benedict method. The Folin-Wu method gave, generally, higher values than the Benedict method, although there was less divergence in the spinal fluid than in the blood analyses. The difference in sugar content obtained by the two methods is not related to the protein or nonprotein nitrogen content of the spinal fluid nor to the nonprotein nitrogen content of the blood.

ARTHUR LOCKE.

REMARKS ON THE USE OF SYNTHETIC MEDIUMS. ALBERT BERTHELOT, Ann. de l'Inst. Pasteur **40**:440, 1926.

Variation in bacterial growth in a given synthetic medium may be due to factors which are difficult to detect, as Berthelot shows in two instances. A certain tyrosine he found is unfit for the cultivation of *Bacillus aminophile* because of the presence of traces of barium. *Bacillus pyocyaneus* develops with abundant pyocyanine formation in a synthetic medium with tyrosine when sterilization at 120 C. has been carried out in a glass which is easily attached, but not when a hard glass is used.

G. B. RHODES.

LÖWENSTEIN-SUMIYOSHI'S METHOD FOR THE CULTIVATION OF TUBERCLE BACILLI. R. MELLER, Ztschr. f. Tuberk. **44**:387, 1926.

The sputum is thoroughly mixed with a threefold amount of 15 per cent sulphuric acid and centrifuged soon enough to allow the contact of the acid with the sputum not longer than fifteen minutes. The supernatant fluid is discarded and the sediment washed three times with physiologic sodium

chloride. The final sediment is planted on potatoes treated with glycerol. The results with this method were as follows: Cultures were obtained twenty-six times out of twenty-seven specimens of urine which contained bacilli microscopically and fifteen times out of thirty-three specimens of urine in which microscopic examination did not reveal any tubercle bacilli. All of thirty-eight positive sputums yielded cultures; of fourteen negative sputums, 5 yielded cultures. This method seems to be important particularly in cases in which tubercle bacilli are found which are not pathogenic for guinea-pigs (Löwenstein). In such cases only a reliable cultural method may give positive results.

MAX PINNER.

THE DIAGNOSIS OF A TUBERCULOUS INFECTION BY STUDYING METHODICALLY THE SEDIMENTATION RATE OF ERYTHROCYTES. L. BÜCHLER and E. NOBEL, Ztschr. f. Tuberk. **45**:7, 1926.

The Pirquet reaction did not influence the sedimentation rate in ten children in whom this reaction was negative. Of fifty children in whom the Pirquet reaction was positive, 60 per cent showed an increase of the sedimentation rate which in some started as soon as four hours after the tuberculin application; frequently no fever or focal reaction was associated. In 4 per cent the rate decreased after a Pirquet test, and in 18 per cent of the patients no influence was observed. Only an increase or decrease of more than 2.5 mm. is diagnostically significant. The authors conclude that an increase in the sedimentation rate after a Pirquet test is rather conclusive for a tuberculous infection, that the lack of such a phenomenon does not prove the absence of an infection, and that this procedure does not allow of a differentiation between active and latent processes.

MAX PINNER.

ON THE TECHNIC OF THE INDIGO-CARMINE TEST WITH SURVEY OF THE EXCRETITON OF INDIGO-CARMINE THROUGH NORMAL KIDNEYS. MASATOKI KOIKE, Tohoku J. Exper. Med. **7**:278, 1926.

The elimination of indigo-carmine through normal kidneys, as determined in twenty cases, begins within five minutes after intravenous injections, ends within three hours, reaches its height within from five to ten minutes, includes about 24.5 per cent of the injected amount within the first fifty minutes, is regular and constant and could be made use of in chromocystoscopy. After intragluteal injections the dye appears first within nine minutes and disappears after six hours; the amount excreted within the first fifty minutes is only 11.1 per cent of the whole amount injected, and the appearance is inconstant.

Society Transactions

COLORADO SOCIETY OF CLINICAL PATHOLOGISTS

Regular Quarterly Meeting Held at the National Jewish Hospital, Denver, Oct. 30, 1926

ANAEROBIC WOUND INFECTIONS IN COLORADO. IVAN C. HALL.

Anaerobic wound infections have received little or no systematic attention in Colorado, although during the last two years, there have been eleven cases of tetanus, with only one recovery, as well as several deaths due to gaseous gangrene following injuries.

Tetanus in these cases originated as follows: tetanus neonatorum (?), 1; lacerating wounds of the feet, 4; frozen feet, 1; splinters in fingers, 1; burn of fingers, 1; influenza and lobar pneumonia, 1; appendectomy, 1; no record, 1.

There seems to be an impression among some physicians that it is unnecessary to use tetanus antitoxin in Colorado, because of the supposed infrequency of the tetanus bacillus in the soil. However, the foregoing cases indicate its presence and point to the necessity of using the same prophylactic precautions in Colorado as elsewhere. The lack of such precautions was evident in several of the detailed reports secured from the physicians in charge of the cases. In some instances, wounds or injuries were treated inadequately by one physician before the symptoms appeared; then a second physician was called, generally too late. In some cases no medical attention had been secured before the symptoms of tetanus appeared. The education of laymen to the necessity of reporting deep wounds for medical attention is emphasized as a problem even more difficult than that of teaching the physician how to treat such wounds.

The recent literature proving the widespread distribution of tetanus bacilli in nature was reviewed with reference to Dr. Hall's experience in the isolation of this organism from the soil in California and from the mouth of a healthy girl, and with particular emphasis on the finding of tetanus bacillus carriers in England by Tullock, in China by Tenbroeck and Bauer and in California by Bauer and Meyer. It would seem that approximately 25 per cent of the population harbors this organism in the intestinal tract.

The occurrence in man of tetanus antitoxin and agglutinins which subdivide the species into seven, possibly eight, serologic types, and the relation of these antibodies to tetanus immunity, was reviewed, with comments on the desirability of confirming and extending the newly found facts in other sections of the world.

The inadequacy of present methods of recording deaths due to gaseous gangrene is deplorable as preventing any statistical analysis to show the importance of this complication of lacerating wounds. The development of the polymicrobic conception of gaseous gangrene was traced, with a discussion of the etiologic causes, their pathologic effects in man and experimental animals and the value of prophylactic serums against them.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, Nov. 11, 1926

EUGENE L. OPIE, *Presiding*

MALIGNANT MELANOTIC TUMORS IN THE NEGRO. JOHN T. BAUER. (From the Ayer Clinical Laboratory, Pennsylvania Hospital.)

Melanotic tumors are seldom found in the negro, and while the course is similar to that of those occurring in the white race, it seems of interest to present two cases which illustrate perhaps a few of the racial characteristics.

The first case was presented by Dr. W. E. Lee before this society about a year and a half ago, but is presented again because the patient was a colored laborer, aged 40, with deeply pigmented skin. He came with signs and symptoms of extreme cardiorespiratory disease and gave a history of having injured his big toe three years previously. This had refused to heal and had been amputated. The stump never healed and about two years after the injury tumors occurred in the regional lymph nodes and later in the lungs, and this led to his death. Necropsy revealed extensive jet black infiltration of the lymphatics of the leg, inguinal glands and lungs with neoplastic tissue. The origin in this case was undoubtedly the toe.

The second case was that of a colored girl, aged 23, who had injured her thumb about fifteen months before admission. The nail had been removed, but the wound had never healed. The axillary lymph nodes were moderately enlarged. The thumb was amputated and the axillary glands removed. Both showed melanotic neoplastic tissue. She still feels well, a year after the operation.

The neoplasm in both instances was melanosarcoma.

The rarity of the occurrence of malignant melanotic tumors in the negro is evidenced by the fact that only fourteen cases have been recorded in the literature, and these tended to develop in those parts of the body which normally contain least pigment. For example, eleven of the fourteen cases give the soles as the site. One occurred on the forehead. The lesion in one of the cases at the Pennsylvania Hospital began on the toe, possibly in the nail bed. The other, too, occurred about the matrix of the nail, which is not deeply pigmented. In the native white people of India it has been noted that melanotic tumors are prone to develop on the soles. White horses develop melanotic tumors more frequently than dark horses. The question as to the rôle that normal pigmentation plays in inhibiting the growth of melanotic tumors naturally arises, and, unfortunately, cannot be answered at present.

Melanotic tumors developing about the matrix of the nail are not infrequent in the white race. As far as can be determined, the case reported now is the first noted in the negro.

Since malignant melanotic tumors are rare in the negro, it is hoped that all future cases will be studied carefully and reported, for the present series is too small to enable one to draw further conclusions.

EFFECTS OF ELEVATION OF BODY TEMPERATURE BY HOT BATHS ON EXPERIMENTAL SYPHILIS IN RABBITS. JAY F. SCHAMBERG and A. M. RULE.

In an effort to shed some light on the manner in which malarial inoculation brings about its favorable effect in neurosyphilis, certain studies on the effect of fever in experimental syphilis in rabbits were undertaken. A group of

rabbits were inoculated intratesticularly with spirochetes and four days later subjected to a series of eleven daily hot baths. The temperature of the water was gradually raised to 45 C. (113 F.), the duration of the bath being about fifteen minutes. An average rise of temperature of about 4 degrees Fahrenheit was brought about. None of these rabbits developed syphilis, although the controls did. This experiment was repeated with the same results.

An effort was then made to determine whether the protection was brought about by the direct elevation of the body temperature or through some indirect means. Emulsions of spirochetes were heated in test tubes on a water bath for different periods: one, two, three, four, five and six hours, respectively, at 40 C. (104 F.), and then inoculated into several rabbits. After heating for one hour, numerous actively motile spirochetes were observed by dark-field examination. Inoculation into rabbits, however, failed to produce syphilis. All emulsions heated for longer periods produced similar results. The spirochetes had been injured biologically so that they were incapable of inducing syphilis. After from four to five hours' heating a slowing in motion occurred, and after six hours at 106 F. motion ceased and there was evidence of breaking up of the spirochetes. In would appear, therefore, that this was the thermal death point.

These results were published in the *Archives of Dermatology and Syphilology*, September, 1926. Another experiment has been carried out since that time to determine the effect of hot baths on primary syphilis in rabbits. Well marked scrotal chancres were produced in a series of rabbits. Twenty-seven days after inoculation, the rabbits were subjected to eleven daily hot baths. At the end of a week, the spirochetes had disappeared and the chancres were healing. At the end of eighteen days, the chancres had completely disappeared. Indeed, the healing was as rapid as after the use of arsphenamine. The controls showed well developed growing chancres at this time. Two months later, the inguinal glands from the treated rabbits were excised and inoculated intratesticularly into other rabbits. These rabbits were free of syphilis at the end of ninety days.

Jahnel and Weichbrodt tried an experiment similar to this in 1919, using dry air heat instead of baths. The chancres were healed much in the same manner. These authors did not, however, demonstrate the cure of the syphilis by lymph gland transplantation.

URINARY CALCULUS IN THE PROSTATIC URETHRA. GIBSON COLBY ENGEL. (From the Lankenau Hospital, Philadelphia.)

A white man, aged 81, who complained of difficulty in passing urine, had not had any urinary difficulties until four months before admission, when he began complaining of frequency and urgency, together with increasing difficulty in starting the stream. This increased until on admission he could scarcely urinate. The urine contained pus, urates and phosphates but no blood. The reaction was at first acid, later becoming alkaline. The staphylococcus was recovered on culture. On attempting to pass a catheter, an obstruction was encountered in the prostatic urethra. However, obstruction to flow of urine was not complete, and operation was postponed on account of the patient's general condition. He developed pneumonia and died four weeks after admission.

At necropsy, the chief lesions were bronchopneumonia, pyonephritis, cystitis, prostatic hypertrophy and urethral calculus. The bladder was filled with thick, purulent fluid. On putting the finger tip into the urethral orifice, a stonelike mass was felt. This was found to be an ovoid calculus, 2 by 1 cm., when exposed by blunt dissection of the prostate, which completely surrounded it.

It was brownish gray and rough, with small nodules all over the surface. The stone was sectioned by embedding in paraffin and cutting with a saw. The central portion was made up of concentric rings of uric acid, while the outer granular portion consisted of phosphate and carbonates.

ROENTGEN-RAY DIAGNOSIS OF BONE TUMORS. R. S. BROMER.

Ashhurst has divided the processes in bone which produce cystic change into three general classes: inflammations, dystrophies and tumors.

Of the inflammations, syphilis produces two kinds of cystic lesions: those occurring under the periosteum in the acute stages of syphilitic periostitis and those seen in the ends of long bones in certain cases of the hereditary form of the disease. These forms are not likely to be confused on the roentgenogram with any of the bone tumors which produce cystic areas.

Chronic osteomyelitis sometimes causes Brodie's abscesses, while together with tuberculosis it often causes the formation of wedge shaped areas, cystic in appearance, in the diaphysial ends of the long bones. The base of such an area usually lies parallel to the epiphyseal line. In these cases, the history is of utmost importance in arriving at a diagnosis (Lovett and Wolbach).

Of the tumors, bone cysts, giant cell tumors and chondromas most frequently are characterized by cystic areas on the roentgenogram. Tumors sometimes occur which seem to be of a transition type. There are lesions which Ewing says are neither benign nor malignant and again there are lesions which are neither granulation tissue, inflammatory reaction nor true tumors. In the progression from inflammatory reaction to malignant neoplasm there are intermediate types. The following are illustrative cases.

CASE 1.—A cystic area was present in the upper extremity of the left femur, showing evidence of chronic inflammatory change in the areas surrounding the lower and inner borders of the cyst, in which there was marked increase in the density of the cortex. The sections from the tissue removed at operation showed the typical appearance of chronic cystic osteitis. The contents of the cyst were hemorrhagic in character, and cultures made at operation from the cyst contents, with all precautions against contamination, showed growths of the staphylococcus.

Phemister has recently isolated *Streptococcus viridans* in two similar cases. These might be regarded as evidence of the inflammatory origin of bone cysts, and might also be regarded as a transition type between chronic osteomyelitis and bone cysts.

CASE 2.—The roentgen-ray appearance of a cystic area in the upper end of the left humerus was that of a bone cyst probably multilocular. The sections showed chronic cystic osteitis with a fairly large percentage of giant cells of the epulis type. These were hardly present in sufficient number to warrant the diagnosis of a giant cell tumor but were certainly more numerous than in the usual picture of chronic cystic osteitis. This case may be regarded as a transition type between a bone cyst and a giant cell tumor.

CASE 3.—In a cystic area in the distal extremity of the radius, the roentgen-ray appearance was that of a giant cell tumor. At the first operation the tumor mass was curetted. The tumor recurred, and one year later was completely resected. The roentgenogram again showed a typical giant cell tumor with an area of increased density of bone at the proximal end of the cyst that might be regarded as evidence of a chronic inflammatory reaction. The recurrent growth showed in many areas a semisarcomatous appearance. The giant cells

were only one-tenth as numerous as on the first sections. This may be regarded as a transition type between a giant cell tumor and a sarcoma.

Case 4.—In a cystic area in the upper third of the humerus, the roentgen ray showed a cystic area with a somewhat curious lobulated appearance of the head. Trabeculations were present. There was not sudden or abrupt expansion of the cortex as is seen in the typical giant cell tumor. There was also a pathologic fracture. The appearance, on the other hand, was not typical of a bone cyst. The sections were diagnosed by seven pathologists as follows: malignant myeloid sarcoma, giant cell tumor, spindle cell sarcoma and xanthosarcoma. This case illustrated the fact that often when there is an atypical roentgen-ray picture the pathologic sections are also of such an atypical nature that they will arouse discussion among competent pathologists.

Conclusion: Bone cysts, giant cell tumors and chondromas show characteristic changes on the roentgenograms and can often be recognized accurately and diagnosed as such. The cases with a typical appearance on the roentgenogram are often characterized by the same microscopic structure. The chondroma undergoing malignant change, as well as the transition or mixed types of the other tumors, offers difficulties for both the roentgenologist and the pathologist. The sequence of cases of such types, from chronic inflammatory reaction through bone cysts, giant cell tumors to actual sarcomas as has been shown could possibly be regarded as evidence of an inflammatory cause of bone cysts, giant cell tumors and certain forms of bone sarcomas.

Roentgen-Ray Appearance of the Normal or Healthy Adult Chest. Henry K. Pancoast.

Under a grant from the National Tuberculosis Association, a committee, composed of F. H. Baetjer of Baltimore, Kennon Dunham of Cincinnati and H. K. Pancoast of Philadelphia, has been studying the roentgen-ray appearance of the normal or healthy chest for six years. The healthy persons have been selected by three internists (C. R. Austrian, Roger Morris and H. R. M. Landis) working with the respective roentgenologists. A report was made on the healthy child's chest in 1922, and the final report on the adult chest was made at the last meeting of the National Tuberculosis Association in October.

This presentation is made as a part of an educational program to spread the knowledge the committee has gained. Two hundred and eighty healthy adults were selected and submitted to roentgen-ray examinations. Observations were made and submitted in the report, which will be published later, as follows: on the bones, the soft parts, the diaphragm, the heart, the aorta, the trachea, the bronchi, the hilum shadows — suggestions as to their boundaries — and the trunk shadows — definite names given to the more important ones. Comment was made on the zones in the lung fields and on the calcifications in the lymph nodes. Observations were made on the lateral view.

Some Attempts to Correlate Roentgen-Ray Appearances with Pulmonary Lesions. F. Maurice McPhedran. (The Henry Phipps Institute, University of Pennsylvania.)

Roentgenograms of inflated excised lungs have been used both as a check and as a standard of detail and contrast to be sought in films of the living. In films of excised lungs, vessels containing blood may be traced out to within 1 cm. of the periphery, where their diameter does not exceed 1 mm. Tubercles measured after section as being 1.5 mm. in diameter may be recorded clearly. These stand out because they are denser than the contiguous tissue. Apical

or right interlobar or lateral pleural thickening measuring 0.5 mm. in depth may be recorded sharply, because it is radiated tangentially; but similar thickening uniformly disposed over the anterior or posterior surface of the lung may not be recognized unless it allows less free entry of air into one lung of a pair, and so increases its density per unit of volume.

When scant apical infiltrations extend into the lung from the pleura the shadow shows a wedge or salient with the base on the pleura. The apex of the salient is directed into the lung substance.

In films of excised lungs, the richness of detail of trunk markings is extraordinary. The interlacing arborizations proceeding from the hilum form a close network. The branching shadows are seen to arise almost entirely from the arterial or venous main stems. Beyond the inner third, the bronchi are lost. This is due to their lesser roentgenographic density. Where the bronchial shadows cross the denser vascular shadows, they are wiped out, and cannot be traced to the periphery. Even in lungs showing purulent bronchitis on section, the bronchial shadow is not to be differentiated. When, however, the bronchi are irregularly dilated and thickened, as in severe chronic bronchitis, the slight increase in density of the wall tangentially radiated and the irregular waviness of the linear shadow make it possible to trace the bronchi to the middle and occasionally to the outer third.

The site of intrapulmonary lymph nodes whether normal or affected by various pathologic changes is not indicated roentgenographically unless the nodes are infiltrated with calcium. The nodes lie lateral to the main stem bronchus on the arterial main stem. Here they do not sufficiently obstruct the roentgen ray to be distinguishable from the shadow of the artery and the venous trunks which cross them converging on the venous main stem. Only if the noncalcium-bearing margin of a node projects laterally to the arterial main stem shadow will it be recorded roentgenographically, contrasting with the air-bearing parenchyma. Usually, calcified nodes are not large enough so to project.

Similarly, even after removal of the great vessels, the site of tracheobronchial lymph nodes, whether fibrous, anthracotic or caseous, is not indicated apart from calcium infiltration. Only calcium is roentgenographically dense enough to cast a shadow which is distinctive in the general shadow of the areolar mantle.

The chest wall, nonpulmonary mediastinal structures and cardiovascular movement prevent obtaining as clear results in the living. Films of emphysematous persons, however, show that the additional ray necessary to penetrate the chest wall does not of itself prevent the recording, in the living, of fine detail.

Tracheobronchial lesions may be studied by oblique exposures whereby the tracheal bifurcation and both bronchi are not obscured by the spine and the manubrium, and even delicate calcium shadows may be differentiated.

Lastly, the major effects of cardiovascular movement may be eliminated by the Weyl pulse relay, diastolic exposures being secured when cardiovascular movement is at a minimum. From such exposures may be made stereoscopic pairs, cardiac volume and the relation of vessels being identical in the two films. The arterial main stem is clearly defined and calcium infiltration of intrapulmonary nodes readily perceptible. Furthermore, in diastolic exposures, blurring and artefacts due to movement are eliminated. Generalized blurring of trunk shadows, to which has been ascribed a pathologic origin, for example, bronchitis or whooping cough, can be shown to be due to systolic

movement. Localized paracardiac blurring in synchronized films in which trunk shadows elsewhere are clear-cut, may be regarded as pathologic in origin, and the cause sought and usually deduced from the films.

The fine aborizations of the normal structure are reinforced by true stereoscopic superposition, and can be traced even through shadows of the ribs, and their symmetrical branchings distinguished from the irregularly disposed densities of early or discrete infiltrations. Earlier diagnosis of infantile types of tuberculosis is possible. These, being chiefly basal, are in the area in which cardiovascular pulsation is most disturbing. Similarly, bronchiectasis is better and earlier discerned.

There is evidence from synchronized exposures that vibration is set up in the lung by the pulse wave and that vibration decreases in amplitude but does not entirely cease during diastole.

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Nov. 16, 1926

PHYSIOLOGIC EFFECTS AND SURGICAL APPLICATION OF LUMBAR SYMPATHETIC GANGLIONECTOMY AND RAMISECTOMY. GEORGE E. BROWN and ALFRED W. ADSON.

Dr. Adson described and illustrated an operation for the relief of vasomotor spasm in Raynaud's disease. A median incision in the lower part of the abdomen allows easy access to the lumbar sympathetic ganglions which are removed from each side at one operation. The operation has not been followed by serious complications in any case.

Dr. Brown discussed the results of the operation. There was immediate relief of the vasomotor spasm. The extremities, which were previously cold and clammy, became dry and warm. There was marked increase in the surface temperature of the feet. Areas of beginning gangrene, when present, soon healed. There was ample evidence, therefore, that Raynaud's disease is a spastic condition of the small arteries, which may be relieved by removing the influence of the vasoconstrictor fibers.

A few patients with Buerger's disease (thrombo-angiitis obliterans) have been subjected to lumbar sympathetic ganglionectomy, and the results have been encouraging. The cases of Buerger's disease selected for operation were only those in which a spastic element could be demonstrated, since it is recognized that this condition is largely due to organic changes in the vessels. To determine this the patient was given an injection of foreign protein (killed typhoid bacilli) sufficient to raise the body temperature a few degrees. This caused a general vasodilation. If the temperature of the foot increased a few degrees in response to this test, a similar vasodilation and increased blood flow resulted from sympathetic ganglionectomy. When definite vasodilation could not be induced, relief could not be expected from the operation.

E. T. BELL, Secretary.

Book Reviews

HYDROGEN ION CONCENTRATION. ITS SIGNIFICANCE IN THE BIOLOGICAL SCIENCES AND METHODS FOR ITS DETERMINATION. By LEONOR MICHAELIS, M.D., Professor in the University of Berlin, Resident Lecturer in Research Medicine in the Johns Hopkins University. Volume I. Principles of the theory. Authorized translation from the second revised and enlarged German edition by William A. Perlzweig, M.A., Ph.D., Associate in Medicine and Chemist to the Medical Clinic in the Johns Hopkins University and Hospital. Pp. 299, including author and subject indexes, and 32 figures. Price, $5. Baltimore: the Williams & Wilkins Company, 1926.

Perhaps no one has contributed more widely than has Professor Michaelis to the biochemical applications of the theory of equilibria in which the hydrogen ion has a part. As a consequence his discussions of theory always have about them the ring of true coin, and the two editions of his Die Wasserstoffionenkonzentration have been found admirably adapted to the biochemical applications of the theory outlined. Therefore, a translation is welcome which will make more easily available to American readers a text already extensively used.

The first chapter of ninety-nine pages covers the main features of the application of the law of mass action to equilibria in systems of acids, bases, ampholytes and their salts. The second deals briefly with the theory of titration, buffer value, etc. The third chapter is, by reason of the date of the German edition, a somewhat inadequate account of "strong electrolytes." This inadequacy is admitted by the author who has interjected a few notes which call attention to the direction of modern trends. An important chapter on the theoretical consequences of ion associations or true salt formation calls attention to a matter which is now being somewhat overlooked. It will serve a useful purpose if it merely stimulates the physical chemist to investigate some of those systems which puzzle the biochemist. The physiologist will regret that the material on dissociation in nonaqueous solutions could be summarized in the five pages of chapter V. Not all phases of cells and tissues are aqueous.

At this point, nearly half way through the book, begins part II, dealing with ions, particularly the hydrogen ion, as sources of potential differences. There is the customary exposition of potential differences at the interfaces between metals and solutions and between solutions of different composition when the solvent is water. Then the author discusses potential differences at phase boundaries. Under this head he discusses membrane potentials, adsorption potentials and indeed a variety of phenomena which are of great importance to physiology. It is regretted that when this material was assembled the time was not ripe for a critical discussion of the possible contribution of the activity concept to these subjects. Perhaps the most noteworthy aspect of part II is the assembly there of material not otherwise easily available.

Throughout the book there are mentioned various biochemical applications, but the subtitle of the book really refers to the series, not yet completed, of which this is volume I. Volume I is essentially concerned with general theory, and comparatively little space is devoted either to specific applications or to methods of measurement. We shall welcome the other volumes when they

appear, but we suspect that the author is putting off the colossal task of summarizing applications. A conservative estimate would be that he would have to assimulate the contents of three thousand papers. This in itself is evidence that the systematic exposition of theory contained in the present volume will be extremely useful.

The translation is, in the main, excellent. Occasionally, as in the subtitle, little traces of teutonic English remain, but because they do not interfere with smooth reading they are rather welcome as evidence of the effort to make a faithful rendition of the original. Indeed, as far as may be judged without minute comparison, the translation is, with unimportant exceptions, faithful. German expressions difficult to render have been handled well. Symbols as well as words have been transformed for the benefit of the English reader but there are still left several equations which would be much more readable were the symbols transformed. S^- for anion and [A] for the sum of anion and undissociated acid are the reverse of the symbolism fitted to the English.

I found few typographical errors. The general appearance of the book is excellent.

They are significant facts that the author of this book holds a medical degree, that his researches have been directed (with ever greater emphasis on fundamental theory) toward the solution of circumscribed aspects of the physical chemistry of life and that the tendency of his experience is toward the emphasis of fundamental chemistry and physics. Let any one ask himself how many substances of biochemical importance are without potentially acidic or basic groups and he will understand not only why Professor Michaelis considers the subject matter of his treatise fundamental, but also why the possession of this classic, now in translation, is almost a necessity to one interested in biochemistry.

ELEMENTS OF PATHOLOGY. By ALLER G. ELLIS, M.Sc., M.D., Rockefeller Foundation Visiting Professor of Pathology and Director of Studies, Medical Department of Chulalongkorn University, Bangkok, Siam. Price, $5. Pp. 544, with 95 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926.

Dr. Ellis' book is divided into two parts, the first dealing with the principles of pathology and the second with postmortem technic and pathologic anatomy and histology. There is no pretense of covering the subject of either portion of the book exhaustively; rather is the volume especially planned to present to the student beginning the study of pathology a good general foundation. This is especially true of the first part of the book. The second part constitutes a well planned and not too cumbersome guide for the performance of postmortem examinations and for the subsequent treatment of pathologic material.

Such a book cannot serve as a substitute for any of the standard reference works on pathology nor is it intended to do so. In fact, references to the literature and discussions of theories are omitted for the purpose of simplicity. The book should prove of value, however, to teachers of classes in elementary pathology and to their students, who are too often confused by a great variety of knowledge. The order of subjects is well planned, and the presentation is clear and understandable. Details of information are usually introduced in the first part of the book only for the illustration of general principles.

The latter portion of the volume will be found useful by the physician who comes in contact with postmortem examinations as well as by the instructor

of elementary classes and by medical students in general. The directions for examining the body on the postmortem table are especially well given.

Altogether the book may be recommended as an excellent introduction to the study of pathology and may be said to live up well to its title.

ESSAYS IN THE HISTORY OF MEDICINE BY KARL SUDHOFF, M.D., Professor of History in the University of Leipzig, 1895-1924. Translated by Various Hands and Edited with Foreword and Biographical Sketch by Fielding H. Garrison, M.D., Lt. Colonel, Medical Corps, U. S. Army. Pp. 397. Price, $5. New York: Medical Life Press, 1926.

The essays by Sudhoff translated in this book are taken mostly from his Skizzen, published in 1921. Some of the sketches in that book dealing with Goethe are replaced with later essays of medicohistorical nature of more immediate interest to the prospective American readers. The difficult task of translation—"Sudhoff's German is the knottiest conceivable"—has been handled by twelve interested persons, almost all well-known students of medical history, and each translation has been revised by the editor with reference to the original meaning. The foreword and biographic sketch by Garrison give a vivid and impressive picture of Sudhoff's arresting personality and his colossal and revolutionary achievement in the history of medicine "which has not been approached in variety, extent and importance by any other medical historian of the past or present." The essays before us represent end-results of Sudhoff's gigantic labors and are of signal value to physicians and others who are interested in medical and cultural history.

THE PRINCIPLES OF ANATOMIC ILLUSTRATION BEFORE VESALIUS. AN INQUIRY INTO THE RATIONALE OF ARTISTIC ANATOMY. By FIELDING H. GARRISON, Lt. Colonel Medical Corps, U. S. Army. Illustrated with 26 full-page plates. Price, $2.50. New York: Paul B. Hoeber, 1926.

If I read this interesting book aright, the message it contains is chiefly to the physician. Though he may not understand, he may yet carefully observe and faithfully describe what he sees. He may thus contribute to the world's knowledge, for his word-picture is based on truth. Before the normal and pathologic processes involved were known, there had been published clinical descriptions of exophthalmic goiter and myxedema that are so accurate that they will stand for all time. In a similar way artists, though ignorant of anatomy, portrayed in carving, drawing or painting figures that are anatomically correct. This was true in the prehistoric and primitive ages of art as well as in the later Hellenistic periods. The portraiture was often of the abnormal such as obesity or achondroplasia. Even in later times, especially in Italy, the artists from a study of the exterior of the body as well as from dissections understood anatomy before the anatomists. The work of the many-gifted Leonardo da Vinci is preemient. Then came Vesalius and modern anatomy.

The purpose of the book, as the author states, is philosophic rather than historical. Rightly to understand it and its many allusions one should have a knowledge not alone of medicine in all its branches, including its historic development, but as well of archeology, anthropology, history, sculpture, painting and the world's best literature; for the volume is written by one of wide learning and of scholarly taste, who does not hesitate to draw for fact or illustration on any science or any art. The style is attractive and one reads because he is interested in the subject and its manner of presentation. At times

the reviewer has reread sentences or paragraphs in order to get the meaning, finding it was his own ignorance that made him fail to understand. At other times he has wondered whether the obscurity was not due in part to an involved and complicated way of saying something that was really simple, a style reminiscent of George Meredith.

The book is well printed and the illustrations are excellently chosen and executed.

PERNICIOUS ANEMIA. By FRANK ALEXANDER EVANS, M.D. Cloth, gold stamped. Size, 6 by 9 inches. P. 170. Bibliography. Baltimore: The Williams & Wilkins Company, 1926.

The reader of this book will find a clear and sharply drawn picture of pernicious anemia. The pathologist may find more than that. The chapter concerning the etiology will point the way for further investigation. Unfortunately, this chapter is not as clear in its exposition as the others; it could advantageously be subdivided into two sections, one dealing with the physiologic pathology and another setting forth the etiology of the disease. The physiologic pathology comprises the reaction of the organism toward some abnormal agent. It is specific and constant for a certain disease. In pernicious anemia, it includes the low values for cholesterol in the blood plasma, the decrease of the cholesterol esters in the red blood corpuscles, the presence of abnormal amounts of hemolytic lipoids in the blood and, further, the achylia gastrica and its relation to the lipoid metabolism. The etiology of pernicious anemia is not known. Hypothetically the cause is ascribed to hemotoxic products of streptococci or of *Bacillus coli* which may form toxic products from meat by putrefaction; or to the increase of the power of the spleen to destroy red blood corpuscles, etc. It is possible that the etiology may vary in different cases.

HYDROGEN ION CONCENTRATION OF THE BLOOD IN HEALTH AND DISEASE. By J. HAROLD AUSTIN, Professor of Research Medicine, University of Pennsylvania, and GLENN E. CULLEN, Professor of Biochemistry, Vanderbilt University Medical School. Price, $2. Baltimore: The Williams and Wilkins Company, 1926.

This book presents in a concise form a review of the results of the investigation of the hydrogen ion concentration of the blood. It is particularly recommended for use in laboratories.

The first chapter deals mainly with a general explanation of the measure of acidity in solutions, the relation between $[H^+]$ and the carbon dioxide combining power of the blood, the significance of buffers, p_H and alkali reserve. In the second chapter the authors dwell on the value p_H of serum and body fluids. The results of the clinical laboratory work on the acid-base-condition (A. B. C.) of the plasma in diseases is discussed in the next chapter. Diseases in which remarkable changes are effected either in the acid base equilibrium or in the p_H concentration of the plasma are: pyloric obstruction, persistent vomiting, uremia, diabetes mellitus, acidosis in children, methemoglobin formation, anaphylactic shock, tetany, disturbances of the parathyroids, etc. The last chapter gives a survey of the most recent methods employed in the determination of hydrogen ion concentration.

The book contains several graphs purposing to simplify the problem. Unfortunately, unless the reader has studied previously writings on the subject, these graphs are not explanatory and are difficult to unravel.

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